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Malnutrition in Cystic Fibrosis in India: Pandora's box

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This is a study conducted with aim to evaluate clinical profile and molecular diagnosis of suspected cystic fibrosis (CF) in Maharashtra, India over a period of two years from January 2012 to December 2014 in the Genetic laboratory of Maharashtra University of Health Sciences (MUHS), Regional Centre Pune. All were tested for DF508 at our laboratory followed by 5 mutational analyses (N1303K, G551D, G542X, 621+1(GT), R553X) at Hinduja Laboratory Mumbai. Our study showed median age group 3.02 year (38 months), recurrent respiratory infection/pneumonia 61.5%,Chronic diarrhea 26.9% with steatorrhea in 7.7%,meconium ileus 11.4%,intestinal obstruction in 15.3 %, CF was diagnosed in 11.4% high risk cases based on sweat chloride test but with ARMS PCR test only 3.8% showed the ΔF508 (homozygous), family history of suggestive of CF with death was present in 3.8%, consanguinity was seen in 6 (23%) patients, clubbing in 3.8%, Malnutrition in 34.6%, *Staphylococcus aureus* colonization in 3.8%, pseudomonas aeruginosa in 3.8%, Ultrasonography findings of our patients showed hyperechogenicity of liver, hepatomegaly and abdominal calcification in 7.6% . Conclusion: As this is a small clinical study, possibility of missing other CF mutations in Indian population cannot be rule out. We suggest extensive molecular analysis of CF in Indian population may throw light on molecular profile of CF patients which will help in genetic counseling and prenatal diagnosis.

Introduction: Cystic fibrosis (CF) is the most common multisystemic genetic disorder amongst Caucasians, affects one in 2500 births, resulting in significant morbidity and mortality. (1) In India cystic fibrosis was supposed to be extremely rare. In majority of cases, it is not suspected or it is misdiagnosed. In majority of cases, when the children are referred for testing, the disease is seen in advanced stage. The knowledge about the incidence and molecular genetics of cystic fibrosis in the Indian subcontinent is limited. In all probability, it may be under reported or diagnosed in late stages. On the contrary, in developed countries early diagnosis and good nutrition, pancreatic enzyme replacement therapy and high fat diet improves the quality of life of CF patients. In developing countries due to limited resources, CF patients have significant undernutrition due to late diagnosis. Recently there have been many reports from Indian researchers which suggest that the disease burden of CF is much more than assumed. (2,3,4).

Kabra et al 2003 studied 120 patients with cystic fibrosis from the All India Institute of Medical Sciences, New Delhi reported recurrent respiratory infection like pneumonia, under nutrition leading to failure to thrive, meconium ileus, malabsorption, rectal prolapse, dehydration, and salty taste on kissing. For proper management of cystic fibrosis patients, early diagnosis is important which can prevent morbidity and mortality (5). These reports suggest that the delayed diagnosis of cystic fibrosis in Indian children lead to severe under nutrition. Under nutrition is one of the poor prognostic indicators for survival of cystic fibrosis patients (6).

Under nutrition leading to failure to thrive (FTT) is very much common in cystic fibrosis patients. Under nutrition occurs in these patients due to many factors like pancreatic enzyme deficiency and intestinal inflammation (7,8). Under nutrition in cystic fibrosis leads to deterioration in lung function, and with increasing age, mortality also increases (9).

It was observed that under nutrition is significant in younger patients. There are possibilities that the children may die due to under nutrition, before they reach adulthood.

Failure to thrive (FTT) is defined as a failure to reach the expected rate of growth for age particularly in early childhood. FTT mostly applies to young infants, affecting cognitive development leading to significant morbidity and mortality. It is defined as weight less than the third to fifth percentile for age on more than one occasion or below 2 major percentile lines as per National Center for Health Statistics (NCHS) growth charts. The symptoms of CF in early infancy include excessive appetite, abnormal stools and failure to thrive. It is suggested to evaluate all children with failure to thrive and malabsorption for cystic fibrosis (10). It is also documented early diagnosis gives better outcome in cystic fibrosis patients (11). Under nutrition was more seen in patients with pulmonary disease (12). It is important to prevent wasting in cystic fibrosis patients by early treatment of lung infections, supplementing digestive enzymes, micronutrient supplements, vaccination and good nutrition.

In view of above the studies, we undertook the study to understand common clinical features of cystic fibrosis with specific reference to under nutrition which are referred by the physicians for genetic test. The results of the study will help in improving management protocol for cystic fibrosis patients in India.

Methodology: The present descriptive prospective study was conducted by Department of Genetics, Immunology, Biochemistry and Nutrition, Regional Centre, Pune, Maharashtra University of Health Sciences (MUHS) after taking ethical approval. The patients suspected CF were referred by physicians from medical colleges, Private and government hospitals in Maharashtra. The clinical symptoms included children with signs and symptoms of cystic fibrosis like failure to thrive, chronic diarrhea, recurrent pneumonia, newborn with meconium ileus, adults with infertility, radiological abnormalities like localized nodular lesions with or without cavitations, segmental pneumonicltrate, patchy interstial or alveolar infiltrates with or without sweat chloride positive test. Patients with HIV positive, Tuberculosis, and malignancy were excluded.

(n=49)					
Sr no	**Clinical Diagnosis**	Males	Females	%	95% CI
1	*Under nutrition	21	22	43 (87.75%)	76.26-94.88
Respiratory involvement (n=63)					
1	Recurrent Respiratory infection	17	10	27 (42.85)	31.09-55.26
2	Pneumonia	10	08	18 (28.57)	18.46-40.61
3	Bronchiectasis	03	01	04 (06.34)	2.04-14.60
	Total	30	19	49 (77.77)	
Gastrointestinal involvement (n=63)					
4	Meconium ileus	04	01	05 (7.93)	2.96-16.71
5	Chronic diarrhea/malabsorption	01	04	05 (7.93)	2.96-16.71
6	Intestinal obstruction	02	02	04 (6.34)	2.04-14.60
	Total	07	07	14(22.22)	
Respiratory and Gastrointestinal involvement					
	*Respiratory infection/Pneumonia/diarrhea	05	01	06(9.52)	3.95-18.76

Table No. 1: Clinical diagnosis of suspected Cystic fibrosis (Age group 0-18 years)

Table no 1 shows the most common presentation of suspected cystic fibrosis is under nutrition followed by recurrent respiratory infection and gastrointestinal involvement. Out of 63 suspected cases of cystic fibrosis, there were 49 cases with anthropometric records and 43 cases (87.75%) had under nutrition that had both respiratory and gastrointestinal complaints. There were 28.5% cases of Pneumonia and 6.3% cases of bronchiectasis which suggest there was delay in diagnosis of respiratory infection which led to pneumonia and bronchiectasis with significant damage to lung parenchyma. In 9.52% cases the patients had both respiratory and gastrointestinal involvement.

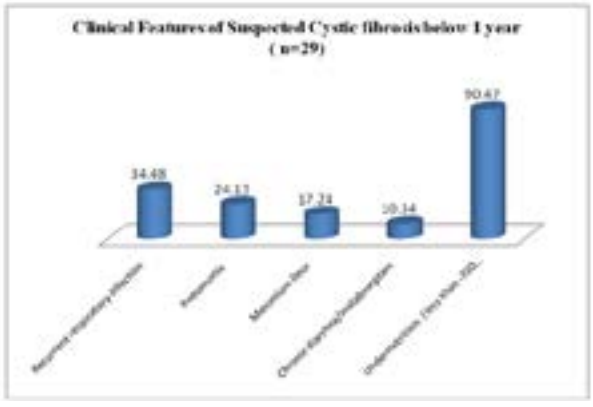

Fig No. 1:

Fig No 1 shows clinical presentations of suspected cystic fibrosis cases below 1 year. Severe acute Under nutrition was recorded in 19 cases (90.47%) which are quite striking. The children with both recurrent respiratory infection and gastrointestinal involvement had under nutrition.

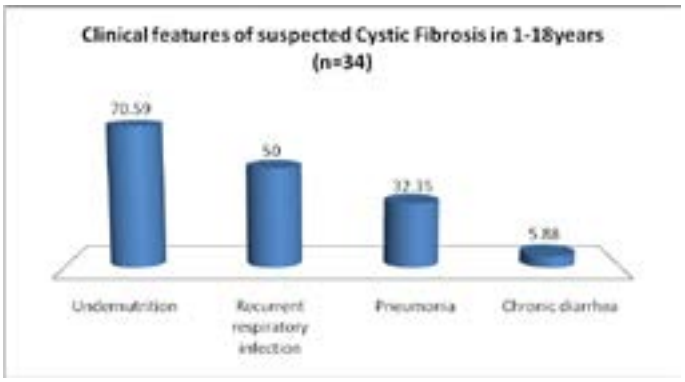

Fig No.2:

Fig No 2 shows clinical presentations of suspected cystic fibrosis cases in the age group of 1-18 years. In this group 70.59% had under nutrition with 50% cases presenting with recurrent respiratory infections and pneumonia in 32.35% cases. Under nutrition and respiratory system involvement is predominant. Gastrointestinal involvement like chronic diarrhea was seen only in 5.9% cases.

Cystic fibrosis, being a serious life limiting genetic disorder, necessitates early diagnosis to improve prognosis. The best approach would be having newborn screening protocol in place. Screening in countries without such a protocol, will have to be based on sweat chloride test. But in the absence of both these facilities, high index of suspicion in clinical practice is important to prevent tragedies in society due to cystic fibrosis. This study is an effort to understand the clinical profile and molecular diagnosis of cystic fibrosis. The study consists of 63 suspected cystic fibrosis patients, with age groups ranging from 0 to 18 years . The study group was then divided into three sets, 0-1 year and >1-18 years. Our study included 29 infants i.e. below one

year of age. Six babies were referred within 15 days of life as suspected cases of cystic fibrosis. This goes to show that high index of suspicion of cystic fibrosis in neonatologists and pediatricians.

In our study though these facilities are not available, high index of clinical suspicion in neonatologists and pediatricians resulted in referral at younger age.

Weight for height data was provided for 49 patients out of 63 patients. Out of the 49 patients, 43 cases (87.75%) had severe acute malnutrition. Out of the 29 infants, who were less than 1 year of age, 8 cases did not have anthropometric record of weight and height. This group had 19 cases (90.47%) severe acute malnutrition in infants. The new WHO growth charts and body mass index charts were used for assessing the nutritional status of children 0-5 years and BMI charts for >5-18 years. Kabra et al 2003 reported under nutrition in 42% patients while Kawoosa et al 2014 reported under nutrition in 100% patients (5,13). In our study we had 87.75% under nourished children in the age group 0-18 years and 35 cases (71.42%) had under nutrition due to respiratory causes but this was not statistically significant.

Under nutrition is quite common in cystic fibrosis. Studies have highlighted that prevalence of under nutrition and lung involvement due to cystic fibrosis increases with age (14, 15). Patients with pulmonary infections have more chances of under nutrition as they need more energy and immunity to fight infections. In majority of cystic fibrosis patients, delayed diagnosis resulted in under nutrition which can lead to progressive pulmonary disease and shortens life span.

Our nutritional assessment has shown 87.7% under nutrition in children as per WHO new growth charts when we analyzed with anthropometric record. Many a times FTT is attributed to nutritional deficiency, rather than cystic fibrosis in India. Early diagnosis helps the cystic fibrosis patients to have better quality of life. It was also found that with better nutritional status, they have less pulmonary involvement and disease progression is less severe (16,17).

There are no specialty clinics for cystic fibrosis which can deliver holistic management for these patients. There are very few diagnostic centers all over the world and hence, emphasis should be on increasing physicians' awareness and use of clinical screening tools. At present, high index of clinical suspicion is mandatory for early detection and prompt treatment intervention.

To conclude it is recommended that cystic fibrosis should be suspected in any case presenting with failure to thrive (FTT) and malabsorption.

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