RESEARCH PAPER

Predictors of Malnutrition in Children with Cystic Fibrosis

NITIN DHOCHAK, KANA RAM JAT, JHUMA SANKAR, RAKESH LODHA AND SUSHIL K KABRA

From Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India.

Correspondence to: Dr Sushil K Kabra, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India. skkabra@hotmail.com

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Objective: To determine occurrence of malnutrition in children with cystic fibrosis and identify predictors of malnutrition at time of enrolment and after 2 years of follow up.

Design: Retrospective chart review.

Setting: Pediatric chest clinic at a tertiary-care center in northern India.

Patients: Cystic fibrosis patients enrolled between 2009-2015 with at least 3 years follow-up.

Procedure: Weight and height were noted at enrolment, and after 1 year and 2 years of follow-up. Clinical details, medications, and pulmonary exacerbations during second year were recorded.

Main outcome measure: Occurrence of malnutrition *i.e.* weight for age Z-score < -2.

Results: 61 medical records were reviewed. Occurrence of malnutrition at baseline, and 1- and 2-year follow-up was 65.5%, 54.1% and 57.3%, respectively. Weight for age Z-score at enrolment significantly correlated with time to diagnosis from onset r=0.015, *P*=0.029). Weight for age Z-score at 2-year follow-up was significantly associated with steatorrhea (*P*=0.03), increased frequency of stools (*P*<0.01) and pulmonary exacerbation (*P*=0.03) during second year. Linear regression showed significant association between weight for age Z-score at 2 years with steatorrhea and pulmonary exacerbations [r=-0.795 (-1.527, -0.062)] and [r=-0.261 (-0.493, -0.028)]. Pulmonary exacerbations during second and third year had significant correlation with weight for age Z-score at the beginning of respective years (r = -0.219, *P*=0.015).

Conclusion: Occurrence of malnutrition is high in children with cystic fibrosis in this region, with uncontrolled fat malabsorption and recurrent respiratory infections being significant risk factors.

Keywords: *Fat malabsorption, Nutrition, Pulmonary exacerbation*.

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Children with cystic fibrosis (CF) are at increased risk of malnutrition due to impaired absorption of nutrients due to pancreatic insufficiency, increased basal energy requirement, and recurrent pulmonary exacerbations, affecting growth. Other co-morbidities like gastro-esophageal reflux disease, CF-related liver disease, and CF-related diabetes can also contribute to inadequate nutrition. Nutritional status is assessed with common anthropometric parameters including weight, height and body mass index (BMI), and calculating Z score from local growth standards [1]. In developed countries, patients with CF have good age-appropriate nutrition with good nutritional intake, pancreatic enzyme replacement therapy (PERT) and high fat diet, but resource-poor countries persist to have significant undernutrition [2-4]. Nutritional status has been associated with respiratory health of the patients and nutritional interventions like high fat/ high calorie diet have been shown to be temporally related with improved nutrition and lung functions in studies from United States and Canada [5].

In India, children are managed with basic cost-effective therapies. Managing nutrition among children with CF in such conditions is further challenging due to delayed diagnosis, inadequate availability of specialist nutritional counselling, poverty, and non-affordability of high cost PERT causing poor control of fat malabsorption, and frequent infections [6]. This predisposes to higher incidence of undernutrition, as seen in other developing countries [4]. There is paucity of studies on the extent of malnutrition and specific predisposing factors operating in Indian subcontinent where CF is still a relatively uncommon and emerging disease. The primary objective of the study was to estimate occurrence of malnutrition in children with cystic fibrosis. The secondary objectives were to determine predictors of malnutrition at the time of enrolment in the clinic, and to determine predictors of malnutrition after completing two years of follow up in the clinic.

METHODS

The study was approved by Institute Ethics Committee of our institute with waiver of need for individual consent. It

was a retrospective chart review where records of all children with CF enrolled in the Pediatric Chest Clinic of a tertiary-care centre in Northern India between 2009 and 2015 were screened. Patients with at least three years regular follow-up (at least two visits per year) after enrolment, with regular weight and clinical records, were included in the study. Cystic fibrosis was diagnosed based on suggestive clinical history and two abnormal sweat chloride assays. Patients were advised a high calorie and high fat diet. Children were regularly followed up in the clinic at intervals of 1 to 3 months (depending on the clinical condition). At each visit, anthropometric measurements, history (details of respiratory and gastrointestinal symptoms) and examination, review of medications and chest physiotherapy, and nutritional counselling were done. Titration of PERT dose for fat malabsorption was done on the basis of level of gastrointestinal symptom control (steatorrhea and diarrhea).

Anthropometric details (weight, and height or length) recorded at enrolment, and at 1 year and 2 year of follow up were noted. Z scores were calculated using age and sex appropriate growth standards using "WHO Anthroplus" software. As weight was the most regularly recorded parameter, weight for age Z score (WAZ) was taken as primary parameter for assessing nutritional status. Patients with WAZ less than –2 were classified as malnourished. Height/ length for age Z score (HAZ) and body mass index Z score (BAZ) were also calculated.

Demographic details, age of onset of symptoms, time taken to achieve diagnosis, sweat chloride value, and reports of the CF gene mutation analysis were recorded for all patients. To identify factors which contributed to poor nutrition in patients despite regular CF-specific therapy, we studied parameters during second year of follow up to identify predictors of nutrition at 2 year. These included gastrointestinal symptoms, details of medications (lipase dose, azithromycin, proton pump inhibitors, multivitamin supplements, nebulisation drugs, and inhaled antibiotics), Shwachman-Kulczycki score [7] and co-morbidities like gastroesophageal reflux disease, CF-related diabetes, CF-related liver disease, intestinal obstruction, and allergic bronchopulmonary aspergillosis (ABPA).

Pulmonary exacerbations were clinically diagnosed based on increase cough, change of nature and amount of sputum, fever, worsening dyspnea, and poor appetite; and treated with either oral or intravenous antibiotics for at least 2 weeks depending on severity of symptoms. Gastrointestinal symptoms (steatorrhea, diarrhea, constipation, inadequate appetite) were considered significant if present on at least two visits in the year. Pseudomonas colonization was considered if two sputum cultures were positive for *Pseudomonas aeruginosa*.

Statistical analyses: WAZ, HAZ and BAZ at enrolment, 1 year and 2 year were compared using Wilcoxon sign rank test. Association between WAZ and predictors were assessed using Spearman's correlation for continuous variables and Wilcoxon rank-sum test for categorical variables, followed by linear regression. Overall correlations between pulmonary exacerbations during second and third year of follow-up with BAZ at the beginning of year were assessed using Spearman's correlation co-efficient. Analysis was done using STATA software (StataCorp, College Station, TX).

RESULTS

Sixty-one children (64% boys) were included in the current study. Most of the children received regular chest physiotherapy (98.3%), 3% saline nebulization (96.7%), PERT (98.3%), azithromycin (96.7%) and fat-soluble vitamin supplementations (96.7%). None of the children received DNase therapy. Median (IQR) number of visits during second year were 4 (3, 5). Baseline characteristics of the cohort are depicted in ***Table* I**. Clinical features during second year of follow up including gastrointestinal symptoms and morbidities are described in ***Table* II**.

WAZ, HAZ and BAZ at baseline, and at 1 and 2 year follow up are described in ***Fig.* 1**. WAZ (P<0.01), HAZ (P=0.02) and BAZ (P=0.005) over first year showed significant improvement. But during the second year, while improvement was not seen in WAZ (P=0.89), HAZ showed improvement (P=0.02) and BAZ showed decline

TABLE I CLINICAL FEATURES OF CHILDREN WITH CYSTIC FIBROSIS AT ENROLMENT TO CHEST CLINIC (N=61)

Clinical features	*No. (%)*
Male	39 (63.9)
#Age (mo)	
At enrolment	22 (7, 60)
At onset of symptoms	2.7 (1, 6)
#Time to diagnosis, mo	19 (5.5, 48)
*Mutation	
Homozygous del508	11 (33.3)
Heterozygous del508	11 (33.3)
Heterozygous 3849+10kb C>T	1 (3.0)
Negative for above	10 (30.3)
$Sweat chloride, mEq/L	103 (27.6)
Meconium ileus	3 (4.9)
Residence outside Delhi	33 (54.1)

**Done in only 33 patients; #median (IQR); $mean (SD).*

TABLE II CLINICAL FEATURES DURING SECOND-YEAR FOLLOW-UP OF CHILDREN WITH CYSTIC FIBROSIS (*N*=61)

Clinical features	*No. (%)*
Gastrointestinal symptoms	
Steatorrhea	20 (32.8)
Constipation	14 (22.9)
Poor appetite	14 (22.9)
Diarrhea	8 (13.1)
Gastrointestinal co-morbidity	
GERD	13 (21.3)
CFLD	9 (14.7)
DIOS	4 (6.6)
Micronutrient deficiency	2 (3.3)
Respiratory morbidity	
Chronic colonization	27 (44.3)
Pseudomonas spp.	26 (42.6)
Staphylococcus spp.	1 (1.6)
ABPA	4 (6.6)
Pulmonary artery hypertension	1 (1.6)
Therapies	
$PERT (lipase units per kg per day)	5684 (4039, 6694)
Inhaled tobramycin	14 (22.9)1
Inhaled colistin	1 (1.6)
Proton pump inhibitors	14 (22.9)
Ursodeoxycholate	8 (13.1)
Second year follow-up	
$Pulmonary exacerbation	1 (0, 2)
Patients hospitalized	9 (14.8)
Shwachman-Kulczycki score	80 (75, 90)
Third year follow-up	
$Pulmonary exacerbation	1 (0, 2)
Patients hospitalized	12 (19.7)

ABPA: allergic bronchopulmonary aspergillosis, CFLD: cystic fibrosis related liver disease, DIOS: distal intestinal obstruction syndrome, GERD: gastroesophageal reflux disease, PERT: pancreatic enzyme replacement therapy.

(*P*=0.02). Occurrence of malnutrition (WAZ <-2) at baseline, and at 1 and 2 year follow up was 65.5%, 54.1% and 57.3%, respectively.

Association of WAZ at enrolment with age of onset of symptoms (r=0.24, *P*=0.07), time to diagnosis (*r* =0.16, *P*<0.001), and sweat chloride (*r* = -0.09, *P*=0.52) was variable. Baseline WAZ was also not associated with gender or place of residence. Linear regression between WAZ with onset of symptoms, time to diagnosis, gender and state revealed only time to diagnosis as significant association (r=0.015, *P*=0.029).

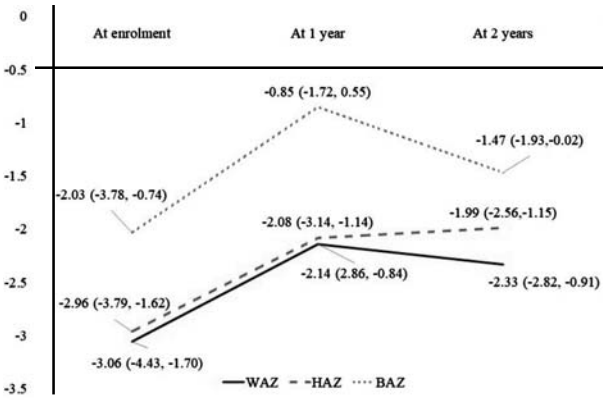

FIG. 1 *Trends of anthropometric parameters. Abbreviations: WAZ: weight for age Z score, HAZ: height for age Z score, BAZ : body mass index for age Z score.*

Correlations between WAZ at 2 years of follow-up with risk factors during second year i.e. numbers of pulmonary exacerbations (r=-0.28, *P*=0.03), PERT (lipase intake per kilogram body weight) (r=-0.25, *P*=0.05), number of oral antibiotic courses (r=-0.31, *P*=0.02), number of IV antibiotic courses (r=0.19, *P*=0.14), Shwachman-Kulczycki score (r=0.19, *P*=0.17), and number of follow-up visits (r=-0.22, *P*=0.09), showed varying results. Association between WAZ at 2 year and morbidities and therapies during second year *i.e.* pseudomonas colonization, proton pump inhibitors use, ursodeoxycholate use, steatorrhea, diarrhea, constipation, appetite, Gastroesophageal reflux disease, CF liver disease, distal intestinal obstruction syndrome, inhaled antibiotics, and pulmonary arterial hypertension had *P*-value of 0.412, 0.686, 0.615, 0.031, 0.004**,** 0.162, 0.571, 0.744, 0.618, 0.704, 0.177 and 0.954, respectively. Since steatorrhea and number of exacerbations were related to diarrhea and number of oral antibiotic therapy, respectively, the former were included

TABLE III LINEAR REGRESSION OF WAZ AT 2 YEARS WITH RISK FACTORS

Variable	*Coefficient*	*95% Confidence interval*	*P-value*
Pulmonary exacerbations in second year	-0.261	-0.493, -0.028	0.029
Steatorrhea	-0.795	-1.527, -0.062	0.034
PERT dose (10^3 units lipase per kg per day)	-0.100	-0.261, 0.061	0.216
Inhaled antibiotics	0.606	-0.189, 1.402	0.133
Constant	-0.904	-1.829, 0.041	0.060

R^2=0.22; level of significance, P-value <0.05. PERT: pancreatic enzyme replacement therapy, WAZ: weight for age Z score.

in regression analysis. Linear regression between WAZ at 2 years and risk factors *i.e.* pulmonary exacerbations, steatorrhea, PERT dose and inhaled antibiotics showed significant association with pulmonary exacerbations and steatorrhea (***Table* III**).

Overall pulmonary exacerbations during second and third year showed significant association with WAZ (r = –0.22, *P*=0.01) and BAZ (r= –0.26, *P*=0.006) at the beginning of second and third year of follow-up; however, similar association was not found with HAZ (*r*=0.07, *P*=0.48). While studying risk factors of pulmonary exacerbation of second year, only WAZ at beginning of second year (*P*=0.03), Shwachman-Kulczycki score (*P*=0.02), and pseudomonas colonization (*P*=0.08) showed significance or trend to significance. Regression analysis of these factors with pulmonary exacerbation during second year demonstrated significant association with only Shwachman-Kulczycki score (*P*=0.02) (***Table* IV**).

DISCUSSION

From this evaluation of hospital records at a referral center, we found that nearly two-thirds of newly enrolled cystic fibrosis patients in our pediatric chest clinic are malnourished. The nutritional status improved over initial one year, probably secondary to the accelerated catch-up growth due to multiple interventions integral to the care of CF children such as chest physiotherapy, PERT, and fat-soluble vitamin supplementation. But the nutritional status did not change much during the second year. This implies that significant proportion of patients stayed malnourished even after starting protocolized CF therapy with good compliance to daily therapies.

Our results are different from that reported from the developed countries. A study from Australia found mean WAZ score -0.14 in 1998 to up to 0.03 in 2014; while another multicentric study from Europe had malnutrition in only 1.9% children [2,3]. Early diagnosis and institution of multidisciplinary care in children diagnosed by newborn screening of CF is associated with improved HAZ and WAZ than clinically diagnosed children [8,9].

TABLE IV LINEAR REGRESSION OF PULMONARY EXACERBATIONS IN SECOND YEAR WITH PREDICTORS AMONG CHILDREN WITH CYSTIC FIBROSIS

Variable	*Coefficient*	*95% confidence interval*	*P-value*
WAZ at 1 year	-0.197	-0.427, 0.032	0.090
Pseudomonas colonization	0.647	-0.038, 1.333	0.064
Shwachman-Kulczycki score	-0.037	-0.069, -0.006	0.020
Constant	3.60	0.858, 6.344	0.011

RV^2 = 0.22; level of significance P value <0.05; WAZ: weight for age Z score.

Scant data are available from developing countries. Of two studies from Brazil, one showed median WAZ ranging from -0.18 in infants to -1.26 in adolescents with progressive worsening with age, while another study reported median BAZ at -0.58. The Shwachman-Kulczycki score in these two studies was also better than our cohort [4,10]. In another study form South Africa, the cohort had only 16% children below the third centile of weight for height [11]. Nutritional status of our cohort is poorer than reports from these developing countries. Overall 35.8% under-5 years children in India have WAZ<-2 as per 2015-2016 survey, which is significantly less than our cohort of children with CF [12].

Nutritional status at enrolment to the chest clinic showed weak positive correlation with time to diagnosis from onset of symptoms. This seems paradoxical as delayed diagnosis should have had worse nutritional [9]. Probably, the patients with delayed diagnosis in our cohort, had less severe disease and hence less malnutrition.

Factors operating during second year of follow-up are likely to impact the growth behavior during second year and hence, nutritional status at 2 years. In our cohort, persistence of fat malabsorption symptoms (steatorrhea and increased stool frequency) and pulmonary exacerbations were independently associated with worse WAZ at 2 years. High cost of PERT makes it difficult to achieve tight control of fat-malabsorption. Lung functions and nutrition are inter-related and follow similar trends; the poorly nourished patients are predisposed to infections, and lung infections negatively impact growth, thereby creating a vicious cycle [13]. Since most of our patients are malnourished and have pulmonary morbidity at the time of enrolment to clinic, it is difficult to establish cause-effect relationship. Aggressive treatment of exacerbations and colonization along with efforts to improve nutritional support should be done to break the cycle of exacerbations and poor nutrition. Apart from the above studied risk factors, lack of specialist CF nutritionist and underlying prevalent malnutrition in our country could contribute to high incidence of malnutrition in our cohort.

Worsening of nutritional status at the beginning of the year is associated with pulmonary exacerbations in the following year in our cohort. Aggressive nutritional intervention for one year in children has been shown to decrease incidence of pulmonary exacerbations [14]. A recent large study demonstrated significantly improved pulmonary function with change in nutritional strategies form restricted fat to high calorie–high fat nutrition [5]. Behavioral therapies, gastrostomy feeding and parenteral

WHAT IS ALREADY KNOWN?

- Improvement in nutritional status is associated with improvement in lung functions in children with cystic fibrosis.

WHAT THIS STUDY ADDS?

- Children with cystic fibrosis in India are at high risk of malnutrition.
- Uncontrolled fat malabsorption is an important predictor of malnutrition in cystic fibrosis.

nutrition are the different modes that have been utilized to improve nutritional status but improvement in pulmonary functions was demonstrated in the study with parenteral nutrition only [15-17]. There is significant scope for aggressive dietary interventions to improve nutritional and pulmonary health in our cohort.

Strength of our study is that the study addresses population from Indian subcontinent where CF is still an emerging condition and patients are managed with inadequate resources; also CF patients in Indian subcontinent are genetically heterogenous from the patients worldwide [18]. Limitation of our study include retrospective study design leading to lack of detailed data on dietary intakes, non-availability of fat malabsorption quantification, and limited availability of pulmonary function test data.

We conclude that malnutrition is common in children with CF in this region, which persists despite protocolized CF care. Inadequate control of fat malabsorption is a significant predictor of poor nutritional health. Recurrent respiratory infections during follow up have significant negative impact on nutritional status. Apart from overall awareness of CF diagnosis and treatment, interventions focused on improving availability and affordability of PERT and reducing infections, along with adequate nutritional support are likely to improve nutritional status in CF children in Indian subcontinent.

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