RESEARCH PAPER

Clinical Profile of Children With Cystic Fibrosis Surviving Through Adolescence and Beyond

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Objective: To document morbidities in adolescents with cystic fibrosis (CF) from India. **Methods**: Details of children with cystic fibrosis surviving beyond 15 years of age were extracted from hospital records, and analyzed. **Results**: 43 children [Median (IQR) age 18.7 (17, 20.6) years, were enrolled. Median (IQR) body mass index was 15.82 (13.5, 19.05) kg/m^2. *Pseudomonas* species were isolated from respiratory specimens of 34 (79%) adolescents. Allergic bronchopulmonary aspergillosis (ABPA) and Cystic fibrosis-related diabetes (CFRD) were seen in 12 (28%) and 11 (26%) patients, respectively. Conjugated hyperbilirubinemia and distal intestinal obstruction syndrome (DIOS) were diagnosed in 15 (35%) and 6 (14%) children, respectively. *Pseudomonas* species colonization (P=0.04) and multiple pulmonary exacerbations in last one year (P<0.001) were significant predictors of FEV_1% predicted. **Conclusion**: Malnutrition, chronic airway colonization, ABPA, CFRD, conjugated hyperbilirubinemia and DIOS are morbidities observed in adolescents with CF in India. The data support the need for early screening of CF-associated morbidities.

Key words: *Allergic bronchopulmonary aspergillosis, Colonization, Cystic fibrosis-related diabetes, Pseudomonas*.

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With the increased awareness and availability of diagnostic tests, the number of children with cystic fibrosis (CF) has been increasing in India [1]. Morbidities increase with age due to the development of complications. Information on morbidities of children with CF surviving beyond 15 years is limited, particularly in resource-limited settings. We share our experience of children with CF who survived beyond 15 years.

METHODS

A review of medical records of children above 15 years of age, with CF, attending the pediatric chest clinic at our tertiary care center from January, 1996 to December, 2019 was carried out. Details of demography, clinical profile, course of illness, and laboratory parameters were extracted. Standard methods were used to diagnose various morbidities like chronic bacterial colonization, pulmonary exacerbation, cystic fibrosis-related diabetes (CFRD), allergic bronchopulmonary aspergillosis (ABPA), distal intestinal obstruction syndrome (DIOS), cystic fibrosis-related chronic liver disease, and bone mineralization disorder in CF [2-5].

Statistical analysis: Appropriate statistical tests were applied, using STATA 12.0 software (StataCorp).

RESULTS

Out of a total of 600 children with cystic fibrosis under follow-up in the Pediatric Chest Clinic since 1996, 43 patients who had survived beyond 15 years of age, with available records, were included in the analysis. Demographic and clinical features are depicted in **Table I.**

The CF-related morbidities detected are depicted in **Table II**. We evaluated correlation of BMI of CF patients with numbers of pulmonary exacerbations in last one year (r=0.26, P=0.08) and FEV_1 % predicted (r=0.37, P=0.01). A higher proportion of children with CF, receiving inhaled antibiotics, had ABPA compared to those without inhaled antibiotics (33% vs 25%, P=0.8). Compared to the children without diabetes, the children with CFRD had higher proportions of positive family history (55% vs 16%, P=0.005), consanguinity (27% vs 6%, P=0.04) and earlier onset of symptoms of CF [median (IQR): 03 (1,6) vs 7.5 (2, 36) months, P=0.06]. One child had multiple episodes of DIOS and all the cases of DIOS were managed conservatively. Nasal polyps were detected in 4 (10%) subjects. One patient, aged 22 years, had given birth to a healthy child.

The median (IQR) FEV_1% predicted of our cohort was 50.5% (30%, 70%). Multivariate linear regression analysis showed that *Pseudomonas* species colonization (P=0.04)

Table I Characteristics of Adolescents With Cystic fibrosis (*N*=43)

Variable	
Age (y)[a]	18.7 (17, 20.6)
Follow-up after 15 y of age (y)[a]	3.6 (2, 5.2)
Male gender	26 (60)
Age of onset of symptoms (mo) [a]	6 (2, 24)
Age at diagnosis of CF (mo) [a]	84 (24, 132)
Delta F508 mutation of *CFTR* gene	9 (21)
Inhaled medication	
Bronchodilator + ICS	38 (89)
Bronchodilator + ICS + mucolytic	4 (9)
Not on inhalation medication	1(2)
Oral azithromycin (immunomodulatory dose)	38 (88)
Inhaled antibiotics	
Total	15 (35)
Tobramycin	7 (16)
Tobramycin and colistin	4 (9)
Vancomycin	2 (5)
Gentamycin	2 (5)
Pancreatic enzyme replacement	40 (93)
Clubbing	39 (90)
Grade 1	21 (49)
Grade 2	3 (7)
Grade 3	15 (35)
Pulmonary exacerbations in last one year	
Nil	14 (33)
1	7 (16)
2	15 (35)
3	6 (14)
>3	1 (2)
PFT[a]	
FEV_1, % predicted	50.5 (32, 70)
FVC, % predicted	64 (46, 78)
FEF, % predicted	28.5 (14, 55)
Chest clearance technique	
Not used	5 (12)
Postural drainage	12 (28)
Self-exercise	17 (40)
Postural drainage+ self-exercise	8 (19)
Acapella	1 (2)

Values in no. (%) or [a]median (IQR). ICS-inhaled corticosteroid.

and multiple pulmonary exacerbations in last one year (P<0.001) significantly predicted FEV_1(% predicted) (r^2=0.52) (**Web Table I**).

DISCUSSION

This study describes the various comorbidities in children with CF surviving beyond 15 years of age. Allergic bronchopulmonary aspergillosis (ABPA), Cystic fibrosis related diabetes (CFRD), conjugated hyperbilirubinemia, and DIOS were the common conditions seen.

Table II Morbidities and Outcome of Adolescents With Cystic Fibrosis (*N*=43)

CF related morbidity	*No. (%)*
BMI during last visit[a], kg/m^2	15.82 (13.5, 19.05)
Chronic bacterial airway colonization	
Pseudomonas spp.	34 (79)
Staphylococcus spp.	15 (35)
Klebsiella spp.	2 (5)
E. coli spp.	1 (2)
Staphylococcus spp.+ *klebsiella* / *E. coli* spp.	14 (33)
Age at first *Pseudomonas spp*. colonization, mo*	48.5 (14, 144)
ABPA (allergic bronchopulmonary aspergillosis)	12 (28)
Age at diagnosis of ABPA, y[a]	13 (11,17)
Pulmonary arterial hypertension	4 (10)
CFRD (Cystic fibrosis-related diabetes)	11 (26)
Conjugated hyperbilirubinemia (>2 mg/dL)	15 (35)
Cholelithiasis	2 (5)
Distal intestinal obstruction syndrome	6 (14)
Rectal prolapse	1 (2)
Osteopenia (assessed by DEXA scan, > grade 1)	2 (5)
Depression	1 (2)
Delayed puberty	1 (2)
Outcome	
Continuing follow-up	31 (72)
Death	2 (5)
Lost to follow-up	10 (23)

All values in no. (%) or [a]median (IQR). ICS: Inhaled corticosteroid; DEXA: dual X-ray absorptiometry; BMI: body mass index.

Recently, Dhochak, et al. [6] demonstrated that recurrent respiratory tract infections were a significant risk factor for poor nutritional status of children with CF. Similarly, we also noticed poor nutritional status of CF patients in this study and almost half of our cohort had two or more episodes of pulmonary exacerbation in last one year of follow-up. The higher proportion of pseudomonas species isolation in these pulmonary infections in our study is explained by the higher age (>15 years) of the patients, who are expected to have developed stable core of pathogenic organism selected over the time with repeated antibiotic exposures during exacerbations [7,8].

The association of ABPA in CF with low BMI, and long term use of azithromycin has been shown in a previous study [9]. Thus, use of azithromycin in majority (88%) of patients, low BMI, in addition to adolescent age group may have been possible contributory factors for higher prevalence rate of ABPA (28%) compared to that (7-9%) reported in Epidemiologic Registry of Cystic Fibrosis [10]. The prevalence of CFRD in our study was slightly higher than

WHAT THIS STUDY ADDS?

- Allergic bronchopulmonary aspergillosis (ABPA), cystic fibrosis-related diabetes (CFRD), conjugated hyperbilirubinemia, and distal intestinal obstruction syndrome (DIOS) were the common morbidities in children with CF who had survived beyond 15 years of age in India.

(21.4 %) in the study done by Jain, et al. [11] from India. Although, statistically not significant, children with CFRD in our study had an earlier age of onset of CF, lower BMI and consisted of a higher proportion of females, which is in line with the results of previous studies [12].

In this study, none of the cases had cirrhosis or portal hypertension but occurrence of conjugated hyper-bilirubinemia and cholelithiasis was almost similar to earlier studies [13]. A different genotype of the Indian children [14], may be one of possible factors for slow progression of liver disease. We observed lower lung functions of our cohort compared to that reported in children of the same age group in CF registries of developed countries [15]. Chronic infection with pseudomonas and multiple exacerbations in the past year were demonstrated as significant risk factors for poor lung functions, in our study.

The limitations of this study are its retrospective design and short duration of follow up. Parameters such as quality of life indices and comorbidities like behavioral changes, psychiatric disorders, osteopenia, infertility and pubertal growth have not been assessed. The small sample size may have overestimated the prevalence of ABPA and CFRD.

In conclusion, this study shows CF-related morbidities are more common in Indian adolescents with CF, with pseudomonas species colonization of airway and recurrent pulmonary exacerbation being important predictors of lung function deterioration. We believe that survival and quality of life can be improved with early recognition and aggressive management of these cystic fibrosis related morbidities.

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Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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