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OXFORD

Course of Illness after Viral Infection in Indian Children with Cystic Fibrosis

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ABSTRACT

Objective: To study the clinical impact of respiratory viral infection in children with cystic fibrosis (CF).

Design: Retrospective cohort study.

Setting: Tertiary care referral centre for CF in India.

Participants/patients: Children with CF attending a pediatric chest clinic.

Methods: Case records of the children with CF who had a pulmonary exacerbation with documented acute respiratory viral infection between October 2013 and December 2014 (Group I) and an equal number of controls (Group II) with pulmonary exacerbation in absence of acute respiratory viral infection were reviewed.

Outcome measures: The two groups were compared for the following outcomes over a period of 12–18 months: bacterial colonization, antibiotics usage, pulmonary exacerbations, numbers of outpatient visits, hospitalization and oxygen therapy and spirometric parameters.

Results: In total, 46 children [23 each with viral infection (Group I) and without viral infection (Group II)] of age 7–264 months were enrolled; baseline clinical status and pulmonary function tests were comparable. Mean (SD) follow-up duration in those who had viral infection and who had no viral infection was 15.7 (7.1) and 17.5 (5.4) months, respectively. On follow-up, children with viral infection (Group I) had adverse outcome in form of greater worsening of Shwachman clinical scores, number of pulmonary exacerbations requiring antibiotic usage [4 (2.1%)] and [2.8 (1.7%)], need for intravenous antibiotics 30.4% vs. 8.7%, hospitalization rates 31.8% vs. 4.3% and mortality 30.4% vs. 4.7%, respectively.

Conclusion: Acute viral infection in children with CF affected course of illness on follow-up, including frequent and severe pulmonary exacerbations requiring hospitalization, intravenous antibiotics, decline in CF scores and increased mortality over next 12–18 months.

KEYWORDS: cystic fibrosis, child, forced expiratory volume, hospitalization, pulmonary function tests, viral infection

INTRODUCTION

Respiratory viral infections can cause significant complications in children with chronic lung diseases and are associated with exacerbations of both asthma and chronic obstructive pulmonary disease [1–3]. Progressive pulmonary damage with eventual

respiratory failure is the major cause of morbidity and mortality in patients with cystic fibrosis (CF); bacterial infections are generally thought to be the major cause of clinical deterioration [4]. However, literature suggests that respiratory viruses do play an important role in pulmonary exacerbations, disease progression and an increase in bacterial adherence to the CF airways [5].

Even with appropriate use of antibiotic therapy, chronic obstructive airway disease continues to develop in patients with CF and is the major cause of morbidity and mortality. In children with CF, approximately half of the pulmonary exacerbations are associated with viral infections and are associated with worsening of spirometric parameters over time, especially in young children [6–10].

If respiratory virus infections do lead to secondary bacterial infection in CF, there may be implications for the management of CF. Hence, we conducted a retrospective cohort study to compare the effects of viral infection on the clinical course of children with CF over a period of 24 months.

METHODS

In this retrospective cohort study, data were collected from the case records of CF patients attending the pediatric chest clinic of an Indian tertiary Care Centre. CF was diagnosed based on typical clinical characteristics and two elevated sweat chloride levels on different occasions. Nasopharyngeal aspirates/nasal swabs of children with CF who presented with pulmonary exacerbations during October 2013 to December 2014 had been tested for viral pathogen using real-time polymerase chain reaction, PCR (Fast-Track Diagnostics, Luxembourg) as a part of another study done at the same institute [B. Arvind, unpublished dissertation]. This PCR test could detect rhino, human corona, influenza A and B, parainfluenza, adeno, respiratory syncytial, human metapneumo and echo viruses. Children with CF were routinely followed up in the pediatric chest clinic every 3 months or earlier if indicated. The clinical information is recorded using a predesigned performa.

Children with CF whose nasopharyngeal aspirates/nasal swabs were tested and found positive for viral infection during an exacerbation were included as Group I. Children with CF and pulmonary exacerbation, whose throat swabs tested negative for viral pathogens were enrolled as controls after matching for age and sex (Group II). The children had been followed up every 3 months or earlier, if needed. Details of the follow-up visits during the 24 months after throat swab collection were collected in a predesigned performa, which included the following: age; gender; weight; height at time of throat swab collection and during follow-up; bacterial colonization; intravenous and oral antibiotics usage; episodes of outpatient visits; hospitalization; percentage of predicted FEV1 (forced expiratory volume in 1 s), FVC (forced vital capacity), MMEF (maximum mid-expiratory flow) and FEV1/FVC for the age and height; and clinical CF score. Clinical CF score designed by Shwachman and Kulczycki [11] was used to assess the clinical status of the children in follow-up. Assessment of pancreatic insufficiency was done with history of frequent, foul-smelling and oily stools. Written informed consent had been taken from parent/guardian before collecting respiratory specimen for viral detection in the earlier study [B. Arvind, unpublished dissertation]. Ethical clearance had been obtained from the institutional ethics committee for the current study. As we collected data from case record forms of children with CF who are routinely followed up in the pediatric chest clinic of the institute, consent for this retrospective study was not obtained from parent/guardian.

Statistical analysis

Data were analysed using STATA ver. 13 (College Station, TX, US) and significance of difference of various parameters between Groups I and II were examined using Student's *t*-test and Mann–Whitney test, according to the distribution of the parameter. Weight for age and height for age *Z*-score were calculated using the Anthroplus software (WHO, Geneva). The visit where throat swab for viral detection was collected was considered as the baseline visit for this study. Multivariate analysis was performed using performing logistic regression model.

RESULTS

Twenty-three children with CF were included in each group. The baseline characteristics of the study children were comparable in both the groups and are

Table 1. Baseline characteristics of the enrolled children with CF (n = 46)

Characteristics	CF children with detection of respiratory virus infection during pulmonary exacerbation (Group I) $N = 23$	CF children without detection of respiratory virus infection during pulmonary exacerbation (Group II) $N = 23$	*p*-value
Age (m) at time of sampling for viral infection, median (IQR)	120 (64, 124)	138 (77, 204)	0.30
Boys, *N* (%)	15 (65.2)	13 (56.5)	0.36
Weight, *Z*-score, median (IQR)	−1.9 (−2.9, −0.63)	−2.8 (−4.3, −0.08)	0.38
Height, *Z*-score, median (IQR)	−1.68 (−3.26, −0.51)	−1.65 (−2.14, 0.17)	0.84
Clinical CF score (SK)			
General score, mean (SD)	21.7 (3.3)	21.9 (2.9)	0.54
Physical examination score, mean (SD)	18.7 (4.2)	19.3 (3.8)	0.64
Nutrition score, mean (SD)	18.6 (3.2)	18.2 (3.2)	0.93
FEV1% at first visit, median (IQR)	56 (28, 80)	41.5 (32, 46)	0.13
FEV1/FVC% at first visit, mean (SD)	95.5 (11.2)	82 (20)	0.15
MMEF % at first visit, mean (SD)	43.5 (25.2)	31.7 (19.8)	0.30

Note: IQR, interquartile range; m, months; SK, Shwachman and Kulczycki; SD, standard deviation; IQR, inter quartile range; FEV1, forced expiratory flow in 1 sec; FVC, forced vital capacity; MMEF, maximum mid expiratory flow.

Table 2. Viruses identified in the enrolled children with CF

Type of virus	Number of children with viral infection, *n* (%)
Rhinovirus	14 (60.8)
Coronavirus	3 (13)
Influenza virus	2 (8.6)
Adenovirus	2 (8.6)
Enterovirus	1 (4.3)
hMPV	1 (4.3)

Note: hMPV, human metapneumo virus.

presented in Table 1. The distribution of viruses detected in the respiratory specimen in the enrolled children is shown in Table 2. The commonest virus detected was rhinovirus (14; 60.8%). Mean (SD) follow-up duration in those who had viral infection and who had no viral infection was 15.7 (7.1) and 17.5 (5.4) months, respectively. Mean (SD) numbers of pulmonary exacerbations requiring antibiotic prescription during follow-up were higher in Group I compared with Group II [4 (2.1) vs. 2.8 (1.7), $p = 0.04$]. Intravenous antibiotic usage and episodes of hospitalizations were significantly more in children who had a viral infection as compared with the others. Mortality was also significantly higher in children in whom virus had been detected (7; 30.4%) as compared with those in whom no virus could be detected in respiratory specimen (1; 4.7%), $p = 0.04$ (Table 3). In total, 14 children in Group 1 and 17 children in Group 2 could perform spirometry and parameters were shown in Table 3. Of the seven children who died in Group I, rhinovirus had been detected in five, adenovirus in one and coronavirus in one during the pulmonary exacerbation evaluated for viral infections. The course of illness of children infected with rhinovirus was compared with those who were infected with other viruses (Table 4). In Group I, three patients were newly colonized with *Pseudomonas aeruginosa* and one patient was colonized with beta-haemolytic streptococcus. Whereas in Group II, three patients were colonized with Pseudomonas and two patients were colonized with *Staphylococcus aureus* after virus isolation. Allergic bronchopulmonary aspergillosis (ABPA) was present in three children in Group I and five children in Group II. One patient was home oxygen-dependent

Table 3. Comparison of course of illness during the follow-up between Groups I and II

Characteristic	CF children with detection of respiratory virus infection during pulmonary exacerbation (Group I) $N = 23$	CF children without detection of respiratory virus infection during pulmonary exacerbation (Group II) $N = 23$	*p*-value
Follow-up duration (months), mean (SD)	15.7 (7.1)	17.5 (5.4)	0.8
Number of OPD visits, median (IQR)	8 (5–9)	5.5 (2–9)	0.6
Wheezing episodes requiring rescue therapy, *N* (%)	13 (56.5)	8 (34.8)	0.17
Weight at end of follow-up, *Z*-score, median (IQR)	−2.27 (−2.73, −0.21)	−2.64 (−3.65, −1.85)	0.38
Height at end of follow-up, *Z*-score, median (IQR)	−2.38 (−3.83, −0.01)	−0.89 (−2.43, −0.08)	0.84
General score, mean (SD)	18.7 (5.3)	22.6 (3.32)	**0.004**
Physical examination score, mean (SD)	17.2 (4.2)	20.6 (3.7)	**0.005**
Nutrition score, mean (SD)	16.1 (4.5)	19.6 (3.3)	**0.004**
FEV1% at last visit; median (IQR)	48 (32, 68)	36.5 (29.5, 48)	0.15
FEV1/FVC % at last visit, mean (SD)	88.7 (18.9)	86.5 (15.4)	0.73
MEF25–75% at last visit, mean (SD)	41.7 (29.4)	31.2 (13.2)	0.18
Number of exacerbations requiring antibiotics (IV + Oral), mean (SD)	4 (2.1)	2.8 (1.7)	**0.04**
Children who received Intravenous (I.V.) antibiotics, *N* (%)	7 (30.4)	2 (8.7)	0.06
Number of exacerbations requiring intravenous antibiotics, median (IQR)	1 (1, 2)	1 (1, 2)	0.22
Number of I.V. antibiotic courses/child-year, median (IQR)	0.6 (0, 1.6)	0.5 (0, 0.8)	0.20
Children who received oral antibiotics, *N* (%)	10 (43.5)	11 (47.8)	0.22
Number of exacerbations requiring oral antibiotics, median (IQR)	3 (2, 4.5)	2 (1, 3)	0.11
Number of oral antibiotic courses/child-year, median (IQR)	1.8 (1, 2.8)	1.2 (0.7, 2.4)	0.13
New bacterial colonization, *N* (%)	4 (17.3)	5 (21.7)	0.44
Change in FEV1% from baseline, median (IQR)	−8 (−17, 3)	−3.5 (−10, 0.5)	0.41
Change in FVC % from baseline, median (IQR)	−9 (−24, 3)	0 (−12, 3.5)	0.33
Hospitalization during follow-up, *N* (%)	8 (38.1)	1 (4.3)	**0.01**
Mortality during follow-up, *N* (%)	7 (30.4)	1 (4.7)	**0.04**

Note: MEF25–75, mid expiratory flow 25-75; FEV1, forced expiratory flow in 1 sec; FVC, forced vital capacity; I.V.,intravenous; SD, standard deviation; IQR, inter quartile range.
Bold values suggest statistically significant difference between the two groups.

intermittently in Group I. Eight children in Group I and one child in Group II required hospitalization at least once during their follow-up. Genetic testing was done in all children for DF508 mutation and four children (8.7%) were homozygous and eight children (17.4%) were heterozygous for DF508 mutation. All the patients were pancreatic insufficient. On univariate analysis, mortality was significantly

Table 4. Comparison of course of illness during the follow-up between the children infected with rhinovirus and non-rhino viruses

Characteristic	CF children infected with rhinovirus, $N = 14$	CF children infected with other viruses, $N = 9$	p-value
New bacterial colonization	1	3	0.29
Number of children with I.V. antibiotic usage	4	3	0.05
Number of children prescribed oral antibiotics	4	6	0.09
Hospitalization	9	3	**0.01**

associated with viral infection ($p = 0.02$) and general examination score ($p = 0.04$) and was not significantly associated with age at the time of CF diagnosis ($p = 0.86$), physical and nutrition scores ($p = 0.26$ and 0.27, respectively) and number of new colonizations ($p = 0.55$). On multivariate analysis by logistic regression model general and physical examination scores [odds ratio, OR 0.4 (0.8–1.99), $p = 0.27$ and 5.3 (0.3–89.9), $p = 0.24$, respectively], new bacterial colonization [OR 2.24 (0.07–67), $p = 0.64$] and presence of viral infection [OR 23.8 (0.8–708), $p = 0.06$] were not associated with mortality.

DISCUSSION

This retrospective cohort study demonstrated that CF children who had suffered a viral respiratory infection had worse outcome in follow-up in the form of lower CF scores, higher use of intravenous antibiotics, higher rate of hospitalization and higher mortality as compared with matched controls who did not have viral respiratory infection.

Respiratory viruses associated with the respiratory exacerbations of CF include influenza A and B, respiratory syncytial virus (RSV), parainfluenza virus (PIV) Types 1– 4, rhinovirus, human metapneumovirus, coronavirus and adenovirus. Viral infections predispose the respiratory epithelium to secondary bacterial infections by multiple mechanisms resulting in frequent pulmonary exacerbations [9, 10]. Rhinovirus has been reported as major viral pathogen in CF with detection rates reaching up to 87% from samples collected both during exacerbations and routine visits [12]. In our cohort too, rhinovirus was the most commonly detected (60.7%) virus. In a prospective multi-birth cohort study by Armstrong *et al.* [6] on viral infection in infants with CF during infancy, 31 children of 101 (39%) were hospitalized for respiratory distress and 16 of them had viral infection, and they concluded that viral infections are important cause of hospitalization in children with CF. Abman *et al.* [13] followed 48 infants with CF over a period of 28.8 months (range 5–59 months); 18 (30%) infants had been hospitalized 30 times for respiratory distress. Among these 18 children, RSV was detected in 7 infants.

Reports from earlier research on CF children have documented that patients with virus-associated infections had higher use of antibiotics at the long-term follow-up, compared with those without virus-associated respiratory tract infections [7, 8]. In our cohort, usage of oral antibiotic was similar in both groups. But the requirement of intravenous antibiotics was significantly higher during follow-up of CF patients with viral respiratory infection compared with those who did not have any virus detected in the respiratory specimen (30.4% vs. 8.7%, $p = 0.06$). In our CF patients with viral infection, 8 of 23 (38%) children required hospitalization for pulmonary exacerbation during their follow-up period, whereas only 1 patient of 23 (4.3%) from the other group required hospital admission. Hospitalization was higher in CF children in whom rhinovirus was detected as compared with other virus.

Over few decades, it has been presumed that viruses may be the harbinger of infection with typical bacterial CF pathogens. A temporal link was proposed between viral infections and new pseudomonas infection [14–16]. There are currently limited data available to determine the effects of viral infection on the CF lung microbiota. *In vitro* studies have shown that RSV and influenza virus increase the adherence of pseudomonas to human airway

epithelial cells and modulate neutrophilic inflammation [10, 17]. It was also shown that RSV promotes growth of pseudomonas biofilms through modulation of the immune response and pathogen iron metabolism [18], while rhinovirus promotes the free movement of Pseudomonas from biofilms [19]. In contrast to what was believed, a recent study on dynamic interaction between respiratory viruses and the lung microbiota in children recently reported that viral infection had no impact on bacterial diversity [20]. In our cohort, three children in each group were found to have new Pseudomonas infection in follow-up, which suggests that viral infection may not be the only factor involved in colonization of Pseudomonas in airway epithelium of CF children.

Viral infections in CF patients are associated with decline in pulmonary function. The majority of studies had shown declining trend of FEV1 and FVC in long-term follow-up in those CF patients who had virus-associated lower respiratory tract infection [7, 21, 22]. Some studies like that by Ramsey *et al.* [8] showed no effect on pulmonary function tests (Vital Capacity (VC) or Residual volume (RV)/Total Lung Capacity (TLC)) in the follow-up of children with CF after viral infection. A recent review on clinical impact of respiratory viruses in CF suggests that high burden of viral respiratory infection in children with CF is likely to be linked with progression of CF lung disease [23]. In our cohort, both the groups had shown decrement of lung function tests over the follow-up period with more decrement in Group 1, though statistically not significant. It suggests that lung disease progresses over the period of time in these patients irrespective of viral infection.

Disease progression in CF is assessed through clinical data, chest radiography and tomography and pulmonary function tests. Shwachman–Kulczycki (SK) [11] score is the most commonly used score to follow the progression of disease activity in CF children. We reviewed clinical data on general activity, physical examination and nutrition in our cohort. At the baseline, both the groups were comparable in above said three domains. However, at the last visit, children in Group I had poorer scores in the domains of general activity, physical examination and nutrition as compared with Group II suggesting that viral infection may play a role in worsening of clinical status in children with CF. Nevertheless, the subjectivity in the score needs to be kept in mind.

Apart from morbidity of CF caused by pulmonary exacerbations, the annual number of exacerbations has a considerable impact on survival also. In our cohort, 87.5% of mortality was constituted by Group I who had viral infection. This can be attributed to the severe pulmonary exacerbations requiring hospitalization in this group of children. In total, 6 of 18 (33.3%) children who required hospitalization in Group I (CF with viral respiratory infection) died by the end of follow-up period. In a predictive model, CF patients who required hospitalization more than twice a year were 3.5 times more likely to die within 2 years [24]. In a similar survival prediction model comprising data from 5820 CF patients selected from Cystic Fibrosis Foundation Patient Registry, each acute pulmonary exacerbation within the first year of follow-up increased the risk of death by 1.5 times in the following 4 years [25]. In a prospective cohort study conducted on 446 adult CF patients, more than two exacerbations per year had a greater risk of lung transplant or death during the study than those with less than one exacerbation per year (adjusted hazard ratio, 4.05) [26]. All of our patients had at least moderate pancreatic insufficiency as suggested by presence of history of frequent, foul-smelling and oily stools. We also note that our patients were malnourished at baseline in both the groups along with low FEV1, which might have contributed to the high mortality in part. Supportive care apart from antibiotics during pulmonary exacerbation plays an important role in the care of CF patients. In our clinic, we do advise and demonstrate regarding chest physiotherapy, inhalation therapy such as hypertonic saline (3% saline) and daily enzyme replacement therapy. However, we do not routinely use DNAse, potentiators or correctors because of cost constraints. We also want to highlight the fact that all of our patients were pancreatic insufficient because patient with milder diseases were not suspected to have CF because of lack of awareness and belief that CF does not occur in Indian children.

Strengths of the study include the use of highly sensitive assay for detection of virus and long-term follow-up of 24 months in Indian children with CF.

The major limitation of the study is its retrospective design. The determination of viral aetiology of pulmonary exacerbation was done only at enrolment; subsequent exacerbations were not investigated for viral etiology.

CONCLUSION

Following the viral respiratory infections in children with CF who were already nutritionally compromised, there were frequent and severe pulmonary exacerbations requiring hospitalization, intravenous antibiotics, decline in CF scores and increased mortality over next 12–18 months.

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