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Case Series

Paediatrics Section

Suspected Cystic Fibrosis in Infantile Onset Pneumonias: A Case Series and Review of Literature

HEMA GUPTA[1], PARASDEEP KAUR[2], RAJESH BETHU[3], PRITI PRIYA[4], ANJU YADAV[5]

ABSTRACT

Pneumonias are common in infancy and infections remain the most common aetiology especially in developing countries. A case-series of 14 children (9 males and 5 females) with cystic fibrosis is presented who came with persistent/recurrent pneumonia. Most children had infantile onset of symptoms (mean age 4.6±4.2 months). Despite multiple medical consultations in infancy, a severe delay in diagnosis (mean age of diagnosis 75.5±65.1 months) and presentation was observed. The youngest child in this series was diagnosed at 2 months of age. Most common manifestations were respiratory, gastrointestinal, and failure to thrive (100%). Sweat chloride test was done in 12/14 children and was elevated in 100%. Genetic mutation was reported in 5 children only. Complications included computed tomography diagnosed bronchiectasis in (7/14; 50%), pseudomonas infections (6/14, 43%); other infections (8/14, 57%), pulmonary hypertension (3/14, 21%), gastroesophageal reflux (2/14; 14%). There was a high (5/14, 35.7%) mortality in this series, as most of them presented late. Lack of awareness and meager diagnostic facilities are major limitations in early diagnosis of cystic fibrosis and may lead to increased morbidity and mortality among these children.

Keywords: Cystic fibrosis trans-membrane conductance regulator, Persistent

INTRODUCTION

Cystic Fibrosis (CF) is an autosomal recessive disorder caused by mutations in gene encoding Cystic Fibrosis Transmembrane conductance Regulator (CFTR) protein causing dehydration of secretions and leading to commonly chronic sinopulmonary disease, pancreatic insufficiency/pancreatitis, neonatal bowel obstruction, rectal prolapse, focal biliary cirrhosis, Failure to Thrive (FTT), and male infertility (obstructive azoospermia). The diagnosis is based on phenotype and genotype characteristics. Specific pancreatic enzyme replacement, CFTR modulators, supplementation of fat-soluble vitamins, salt supplementation, airway clearance, and antibiotics form the mainstay of treatment. The disease is mainly reported in Caucasians in Europe and America (1 in 2,500) with low prevalence in Asia (1:10000 to 1:40750) in the past [1]. In India the first case of CF was reported in 1968, and in children the largest series was published in India by Kabra SK and Kabra Madhulika, [2]. Only few reports from other centers are present from India [3,4]. This series hereby presents children with CF, who reported to the institution in over a decade. Also compares the clinical and genetic characteristics of these children with previous Indian studies.

CASE SERIES

This case series includes 14 children with recurrent pneumonia, who reported to the Paediatric Chest Clinic. All these children were diagnosed with cystic fibrosis. Clinical and laboratory characteristics of children are tabulated in [Table/Fig-1]. Few interesting features are described below.

Baseline clinical and demographic characteristics: There were nine males (64.2%) and five females (35.8%), and most of the children were from outside Delhi (6/14). The age range was 2-24 months, with early onset of symptoms (30% neonatal, 40% between 1-3 months and 30% between 3 months-1 year). There was a considerable lag in diagnosis, with only 2 children diagnosed in infancy. Two children were diagnosed at 2 months of age.

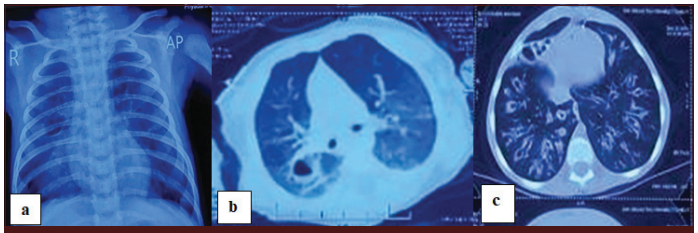
Parameters	Findings
Male:Female	1.8:1
Local residents n (%)	6 (43%)
Age of onset of symptoms (months) (Mean±SD)	4.6±4.2 0.2 months to 12 months
Main symptoms and signs	
1. Respiratory symptoms n (%)	14 (100%)
2. GIT/Other symptoms n (%)	6 (43%)
Age of diagnosis (months) (Mean±SD)	75.5±65.1
Lag in diagnosis (months) (Mean±SD)	70.9±59.9
Family history	
1. Consanguinity n (%)	1 (7%)
2. Sibling death n (%)	2 (14%)
Failure to thrive n (%)	14 (100%)
Clubbing n (%)	11 (79%)
Anaemia n (%)	13 (93%)
Rickets n (%)	13 (93%)
Antitubercular therapy n (%)	7 (50%)
Bronchiectasis on CT chest n (%)	7 (50%)
Sweat chloride (meq/L) (Mean±SD)	92.5±35.7 Range-66 to 180 (not performed in two cases)
Stool fat n (%)	2 (14%)
ABG alkalosis n (%)	3 (21%)
Hyponatraemia n (%)	1 (7%)
Hypokalaemia n (%)	2 (14%)
Genetic mutation	5/14 (CFTR 1265C, delta 508 in 2, 3849 in 2) 1 case×28 duplication

Complications	
Pseudomonas infection n (%)	6 (43%)
Sinusitis n (%)	1 (7%)
Allergic bronchopulmonary aspergillosis n (%)	8 (57%)
Pulmonary hypertension n (%)	3 (21%)
GER n (%)	2 (14%)
Other infections n (%)	8 (57%) (Staphylococcus, Candida, Prevotella, Candida, Klebsiella)
Mortality n (%)	5 (36%)

[Table/Fig-1]: Baseline clinicolaboratory characteristics of children.
*Mean levels of sweat calculated on basis of one highest value of patient; GIT: Gatrointestinal tract; CT: Computed tomography; ABG: Arterial blood gas; CFTR: cystic fibrosis transmembrane conductance regulator; GER: Gastroesopageal reflux

The youngest infant was 2-month-old and presented with recurrent episodes of high-grade fever, cough, and fast breathing since day 15 of life. Each episode lasted for 5-6 days with history of 3 hospitalisations till date. There was history of oily stools present for 1 month of age and one elder sibling died, owing to meningitis at 1 year of age. On examination, child had pallor, heart rate (114/min), respiratory rate (56/min, respiratory distress+ with intercostals retractions), Oxygen Saturation (SpO_2) 94% at room air, and weight 3.9 kg (-2 to -3 SD). Chest examination revealed bilateral diffuse crepitus and rhonchi. Investigations revealed haemoglobin to be 11.1 gm/dL, total leukocyte count (15200/mm^3), and the tuberculosis work-up (Gene Xpert, X-ray chest) was negative. The gastroesophageal reflux scan, Toxoplasmosis, Rubella Cytomegalovirus, Herpes simplex, and HIV (TORCH), urine test for Cytomegalovirus (CMV) and work-up for mycoplasma, legionella and chlamydia were negative.

In view of recurrent infections and sibling death, the possibility of immunodeficiency disorder was kept and immunology work-up was negative (immunoglobulin level, flow cytometry). Radiographs [Table/Fig-2a] and Contrast Enhanced Computed Tomography (CECT) Chest [Table/Fig-2b] showed bilateral areas of lower lobe consolidation with a single cystic lesion in right lower lobe. Thus, a possibility of congenital malformation like congenital pulmonary airway malformation was considered [Table/Fig-2c]. In view of recurrent pneumonia and oily stools, CF was done. Stool test for fat globules was positive, and arterial blood gas analysis showed metabolic alkalosis and hypochloraemia, while sweat chloride was increased on 2 separate occasions (77, 100 meq/L). Molecular diagnosis for CF was positive for heterozygous delta F 508 (c1521-1523 del CTT). This was one of the youngest children in this series, and surviving to date.



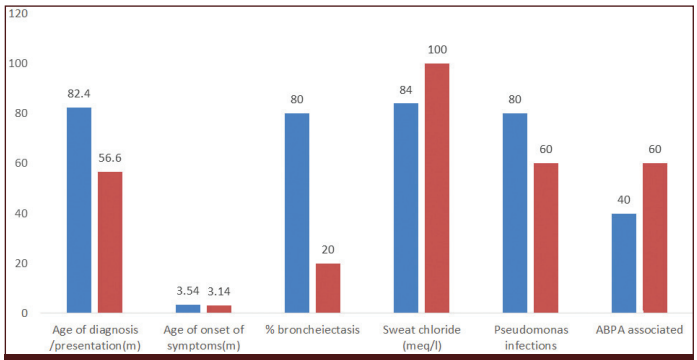
[Table/Fig-2]: (a) Chest radiograph showing bilateral haziness and cystic lesion in right middle zone. (b) finding on CECT showing bilateral consolidation and cystic lesion. (c) showing chest CT with bilateral cylindrical and traction bronchiectasis.

Almost all children presented with known respiratory and gastrointestinal symptoms. On clinical examination, most of the children had failed to thrive, clubbing, rickets, and anaemia. History of consanguinity was present in only one child and none had affected sibling with CF. Two children had a history of sibling death and almost all children presented with known respiratory and gastrointestinal symptoms. On clinical examination, most of the children had failed to thrive, clubbing, rickets, and anaemia. History of consanguinity was present in only one child and none had affected sibling with CF. Two children had a history of sibling death due to other causes. Unfortunately, 50% of the children received antitubercular therapy of which one child received ATT 3 times without any evidence except clinical persistent symptoms.

Diagnostic evaluation: Children with known phenotype and 2 positive sweat chloride suggestive of CF or genetic mutation was diagnosed with CF [5,6]. In children with phenotype of CF two values of increased chloride in sweat were documented in 9 children by pilocarpine electrophoresis [Table/Fig-1]. The results of sweat analysis were conclusive of CF (Cl >60 meq/L in children beyond neonatal age) except for two on whom the test could not be done. In this case, the phenotype presence of Allergic Bronchopulmonary Aspergillosis (ABPA) with bronchiectasis (ruling out tuberculosis, hyper Immunoglobulin E syndrome, HIV, untreated and severe asthma) and genotype supported the diagnosis. Other screening tests like stool fat and metabolic alkalosis and electrolyte abnormalities were not of much help in the series. It was observed that in all children there was huge gap in age of presentation or onset of symptoms versus age of diagnosis [Table/Fig-1].

Bronchoscopy was done in all patients and suggestive of dirty secretions and collapse in few and child 10 had shown severe mucus plugging. High incidence of complications like ABPA and pseudomonas infection was present in this series. None of the children had other CF-related systemic complications, like, liver disease or diabetes.

Children who died had lower sweat chloride levels (84 meq/L vs. 100 meq/L), a late age of diagnosis (82.4 months vs. 56.6 months), higher incidence of pseudomonas infection (80% vs. 60%), and bronchiectasis on chest CT (80% vs. 20%) as compared to those who survived [Table/Fig-3].



[Table/Fig-3]: Comparison of parameters in children who died (blue) vs. those surviving (red).

DISCUSSION

In this series of 14 children, all had onset of symptoms in infancy but only 30% were diagnosed in infancy despite multiple hospital visits. The mean age of diagnosis was 75.5±65.1 months, with a considerable lag in diagnosis (range 2.5 months to 24 months). However, these results are from a very small population and hence cannot be generalised. In this series, sweat chloride estimation with phenotype could confirm diagnosis in 92.8% cases and genetic mutation was helpful in 5/14 cases. Genetic mutations were identified in five, suggestive of CF. Besides delta 508 (n=2) and 3849 (n=2) mutations, one child showed CFTR-EXON 10; C1265C>C/T(P ser

422 Phe) which has not been previously reported. One child, with phenotype and sweat chloride levels suggestive of CF, had Xq 28 duplication. In this child there was deaf-mutism, rocker bottom foot, knee contractures, deformities, and intellectual disability. These features were not previously reported with CF and seems to be an incidental finding rather than an association.

The findings are comparable with other Indian reports. The study by Shastri SS et al., on 100 children reported mean age of diagnosis to 52.7 months, mean age of onset of symptoms at 10.7 months, mean sweat chloride levels of 97.6 meq/L, consanguinity in 13%, failure to thrive, gastrointestinal and respiratory manifestations in almost all (97%) with associated staphylococcal (11%), and Pseudomonas infections (46%) [7]. Similar results from Chandigarh on 27 children reported a mean age of onset of symptoms as 11±3.3 months [8]. Respiratory and gastrointestinal manifestations were common in 92.6% and 88.9%, respectively. Another study from Kashmir reported CF in three (0.8%) patients with median age of presentation of 78 months [3]. Family history suggestive of CF was present in one (33.3%) and consanguinity in three (100%) patients. Common clinical manifestations at the time of presentation included recurrent pneumonia in three (100%), failure to thrive in three (100%), and recurrent diarrhoea in one (33.3%) patient. General physical examination showed pallor in three (100%), malnutrition in three (100%), and clubbing in two (66.7%) patients. Staphylococcus aureus was cultured from sputum in one (33.3%), pseudomonas aeruginosa in one (33.3%) patient. Delta F508 mutation was present in one (33.3%) patient [3].

Few studies have correlated sweat chloride levels, morbidity and mortality in children with CF. A study from Kashmir was conducted on nine borderline and 41 elevated sweat chloride levels subjects [9]. It concluded that elevated sweat chloride levels were significantly associated with wheeze, FTT, history of CF in siblings, product of consanguineous marriage, digital clubbing, and steatorrhea on univariate analysis. On multivariate analysis, only wheeze, FTT, and steatorrhoea was found to be significantly associated with elevated sweat chloride levels. Among the nine borderline cases, six were positive for atleast two CFTR mutations. Different genetic mutation studies have reported AF508 mutation in 19-56% Indian patients [10,11]. The largest study from India by Kabra M et al., (120 children with CF) reported Delta 508 as the most common mutation (40% positive) [12]. Phenotype genotype correlation showed that pF 508 deletion was associated with severe disease and early age of onset [7].

CONCLUSION(S)

In children with recurrent respiratory manifestations a high index of suspicion must be kept for CF, as an early diagnosis may limit unnecessary ATT, mortality, and morbidity in these children. With limited availability of universal newborn screening, sweat chloride test and financial limitation of mutational studies for early diagnosis of CF, the resources should be enhanced in India and other developing countries.

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PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Paediatrics, ABVIMS and Dr. Ram Manohar Lohia Hospital, New Delhi, India.
2. Senior Resident, Department of Paediatrics, ABVIMS and Dr. Ram Manohar Lohia Hospital, New Delhi, India.
3. Resident, Department of Paediatrics, ABVIMS and Dr. Ram Manohar Lohia Hospital, New Delhi, India.
4. Resident , Department of Paediatrics, ABVIMS and Dr. Ram Manohar Lohia Hospital, New Delhi, India.
5. Senior Resident, Department of Paediatrics, ABVIMS and Dr. Ram Manohar Lohia Hospital, New Delhi, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Hema Gupta ,
H34/70, Sector 3, Rohini, Delhi, India.
E-mail: hema_g10@hotmail.com

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