Underlying Diseases Associated with Persistent Pneumonia in Children Aged 2 Months to 5 Years

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Abstract:

Background: Persistent pneumonia in children pose a significant challenge to the pediatricians as there are underlying reasons of persistence. There are limited data on the underlying diseases predisposing to persistence of pneumonia in children. Objective: To identify the underlying diseases of persistent pneumonia in children. Methods: The cross sectional observational study was conducted at Bangladesh Shishu (Children) Hospital & Institute from November, 2019 to October, 2020. Children 2 months to 5 years of age admitted with persistent pneumonia were analyzed to find out the underlying diseases.

Results: Among 49 cases of persistent pneumonia, underlying disease could be determined in 41 (83.7%) cases. The diseases were cystic fibrosis 13 (26.5%), congenital heart disease 10 (20.4%), primary immunodeficiency 10 (20.4%), gastro-esophageal reflux disease 5 (10.2%), pulmonary tuberculosis 4 (8.1%) and congenital anomalies of respiratory tract 1 (2%).

Conclusion: The most common underlying diseases of persistent pneumonia are cystic fibrosis, congenital heart disease, primary immunodeficiency followed by gastro-esophageal reflux disease, pulmonary tuberculosis and congenital anomalies of respiratory tract.

Key words: Congenital heart disease, Cystic fibrosis, Persistent pneumonia, Primary immunodeficiency, Pulmonary tuberculosis.

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Introduction:

Pneumonia is the most common cause of morbidity and mortality in children younger than 5 years.[1-3] In Bangladesh, 13% of under 5 mortality occurs due to pneumonia.[1,3] Approximately 1 out of 10 children of pneumonia develop recurrent/persistent pneumonia.[4] Persistent pneumonia in children pose a significant challenge to the pediatricians and respiratory physicians[5] as there are underlying reasons of persistence. The underlying factors are congenital malformations of upper or lower respiratory tract and thoracic cage, congenital heart diseases, pulmonary tuberculosis, aspirations, defects in clearance of airway secretions specially in cystic fibrosis and other ciliary dyskinesias, primary or acquired immunodeficiency, foreign body aspiration, inadequate antibiotic therapy, pneumonia with atypical organisms and/ or resistant organism.[5] There are limited data on the underlying diseases predisposing to persistence of pneumonia in children specially in developing world. [5,6,7,8,9] Identification of the underlying diseases can facilitate prevention, early diagnosis and management of persistent pneumonia in children.[4] The aim of this study is to find out the underlying diseases of persistent pneumonia among children admitted at a tertiary care pediatric hospital.

Methodology:

The cross sectional observational study was conducted at Bangladesh Shishu (Children) Hospital & Institute from November, 2019 to October, 2020. Children 2 months to 5 years of age admitted with persistent pneumonia were analyzed to find out the underlying disease. Persistent pneumonia was defined as features of lower respiratory tract infection (cough, tachypnoea and fever with or without chest retractions) with radiological evidence of infiltrates or consolidation in the lungs

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persisting for 30 days or more, despite receiving antibiotics for a minimum period of 10 days. Children who had history of prolonged mechanical ventilation during neonatal period were excluded.

Data were collected from the legal guardians by interview and by physical examination of the children and from investigation reports and were recorded systematically in a questionnaire. Complete Blood Count, serial chest X-ray, gastric lavage for AFB and GeneXpert, Mantoux test, echocardiography and HIV screening were done in all patients. Serum immunoglobulin levels were estimated in patients having history of recurrent severe bacterial infection or infection at multiple sites. Primary immunodeficiency panel by flow cytometry was done in patients with low level of serum IgG or IgM and low lymphocyte count. It was done in the Department of Microbiology & Immunology, BSMMU. Other investigations like CT scan of chest, sweat chloride test (Pilocarpine iontophoresis), contrast oesophagogram were individualized according to clinical suspicion. Patients having low levels of Serum Immunoglobulins and/or T-cell, B-cell or NK-cell markers detected by flow cytometry were diagnosed as primary immunodeficiency. Those with persistent radiologic opacity with positive sweat chloride test on two separate occasions were considered as cystic fibrosis. The study was approved by the Institutional Review Board (IRB) of Bangladesh Shishu (Children) Hospital & Institute. Informed written consent was obtained from the parents.

Data were analyzed using computer software SPSS (Statistical package for social sciences) version 23.

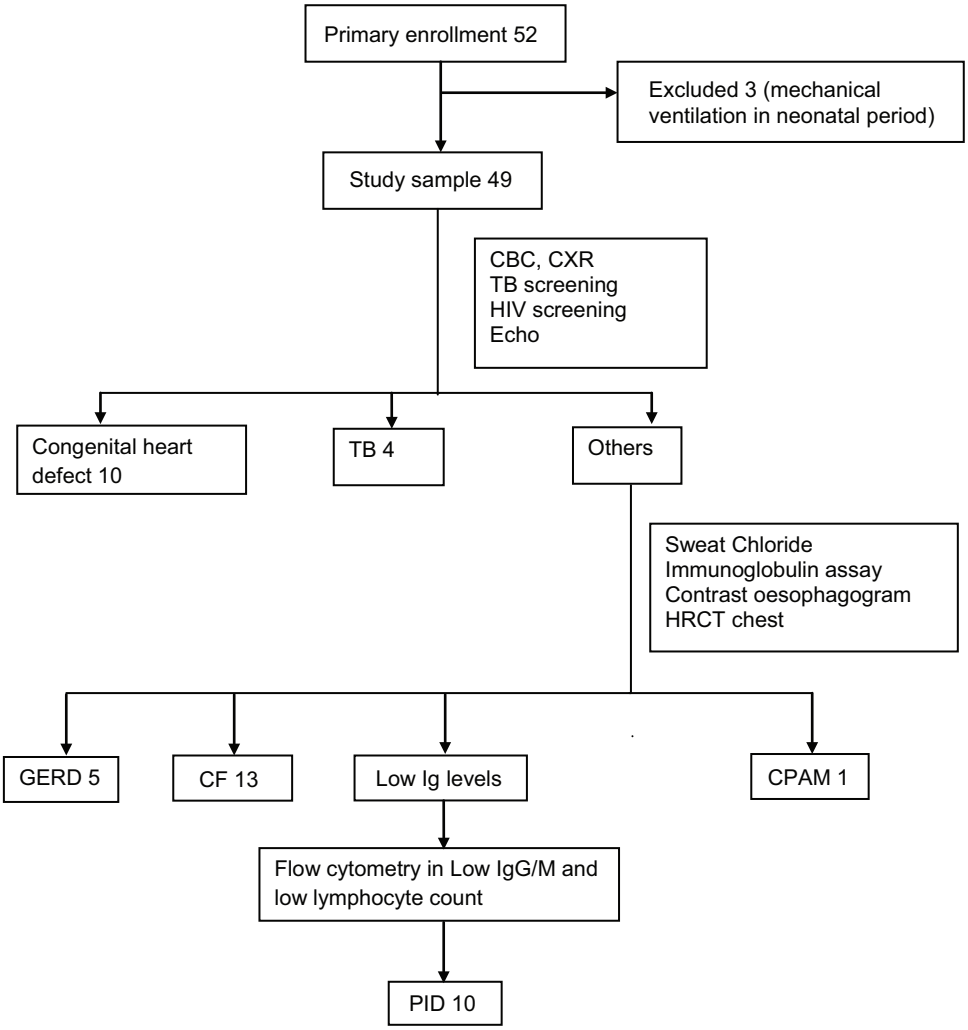

Figure 1: *Flow diagram*

Results:

A total of 52 cases of persistent pneumonia were initially enrolled. 3 children having history of mechanical ventilation during neonatal period were excluded. Remaining 49 children with persistent pneumonia were analyzed (Figure I). The median age of the patients was 8.0 months where majority (75.5%) were male (Table I). In 41 (83.7%) cases, underlying disease could be identified.

The chest radiographs showed evidence of pneumonia in all cases. Bronchopneumonia was found in 31(63.3%) patients and aspiration pneumonia evidenced by right upper lobe consolidation was found in 5(10.2%) patients. Beside these, 4(8.2%) had lobar pneumonia, 4(8.2%) had collapse and 2(4.1%) had bronchopneumonia with pleural effusion. Few had bronchiectasis (2.0%), bronchopneumonia with pneumothorax (2.0%) and bronchopneumonia with cardiomegaly (2.0%) (Table II).

Among the 49 cases, 13(26.5%) patients had cystic fibrosis, 10(20.4%) patients had congenital heart disease, 10(20.4%) patients had primary immunodeficiency, gastro-esophageal reflux disease was present in 5(10.2%) patients and pulmonary tuberculosis was present in 4(8.2%) patients. In 8(16.3%) patients, no underlying disease could be identified (Table III).

Sweat chloride test was performed in 30 patients. 16(53.3%) of them had normal sweat chloride test while 13(43.3%) had positive sweat chloride test. 1(3.3%) patient had intermediate value (Figure II).

Echocardiography showed 3(6.2%) patients had Atrial Septal Defect (ASD), 2(4.1%) had Ventricular Septal Defect (VSD), 2(4.1%) had both ASD and VSD, 1(2%) had Patent Ductus Arteriosus (PDA), 1(2%) had both ASD and PDA and 1(2%) had both VSD and PDA while 39(79.6%) patients were normal in echocardiography (Table IV).

Primary immunodeficiency was diagnosed in 10(20.4%) patients by interpreting serum immunoglobulin assay and flow cytometry. Serum immunoglobulin assay was performed in 34 patients. 26(74.5%) of them had normal immunoglobulin levels. Reduced serum IgA was found in 3(8.8%) patients while 2(5.9%) patients had reduced serum IgG, 2(5.9%) had reduced serum IgM and 1(2.9%) had reduced serum IgG and IgA (Table V). Nine patients underwent flow cytometry; among them 2(22.2%) had normal flow cytometry while 7(77.8%) patients had abnormal flow cytometry. Among the abnormal flow cytometry, 6(66.7%) had severe combined immunodeficiency and 1(11.1%) had X-linked agammaglobulinemia (Table VI, VII). None of the patients were HIV positive.

Gastro-oesophageal reflux disease (GERD) was diagnosed in 5(10%) patients. Contrast oesophagram was performed in 9 patients. Among them, 4(44.4%) patients had normal findings while 5(55.6%) had gastro-esophageal reflux.

Pulmonary tuberculosis was diagnosed in 4(8.2%) patients by GeneXpert from gastric aspirate and positive Mantoux Test.

Congenital pulmonary airway malformation was found in 1(2%) patient by CT scan of chest.

Table I

Distribution of patients by socio-demographic status (n=49)

Socio- demographic status	Frequency (n)	Percentage
Age (in months)		
2-6	20	40.8
7-12	16	32.7
13-59	13	26.5
Median [IQR]	8.0 [3.7, 12.5]	
Gender		
Male	37	75.5
Female	12	24.5
Monthly family income (in taka)		
10,000-15,000	11	22.4
16,000-30,000	33	67.3
>30,000	5	10.2
Median [IQR]	20,000.00 [20,000, 25,000]	
Consanguinity		
Absent	44	89.8
Present	5	10.2

Table-II

Distribution of patients by chest radiograph (n=49)

Chest radiograph	Frequency (n)	Percentage
Bronchopneumonia	31	63.3
Aspiration pneumonia	5	10.2
Lobar pneumonia	4	8.2
Collapse	4	8.2
Bronchopneumonia with Pleural effusion	2	4.1
Bronchiectasis	1	2.0
Bronchopneumonia with pneumothorax	1	2.0
Bronchopneumonia with cardiomegaly	1	2.0

Table-III

Distribution of patients by underlying illness (n=49)

Underlying illness	Frequency (n)	Percentage
Cystic fibrosis	13	26.5
Congenital heart disease	10	20.4
Primary immunodeficiency	10	20.4
Gastro-esophageal reflux disease	5	10.2
Pulmonary tuberculosis	4	8.2
Congenital lung anomalies	1	2.0
Unknown cause	8	16.3

Multiple response

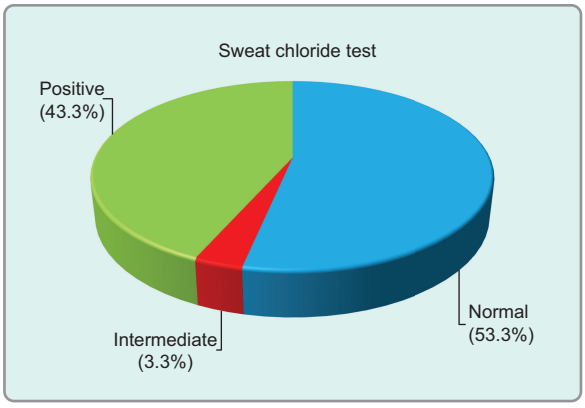

Figure 2: *Distribution of patients by sweat chloride test (N=30)*

Table-IV

Distribution of patients by echocardiography (N=49)

Echocardiography	Frequency (n)	Percentage
Normal	39	79.6
Atrial Septal Defect (ASD)	3	6.2
Ventricular Septal Defect (VSD)	2	4.1
ASD and VSD	2	4.1
Patent Ductus Arteriosus (PDA)	1	2.0
ASD and PDA	1	2.0
VSD and PDA	1	2.0

Table-V

Distribution of patients by serum immunoglobulin assay (N=34)

Serum immunoglobulin assay	Frequency (n)	Percentage
Normal	26	74.5
Reduced IgA	3	8.8
Reduced IgG	2	5.9
Reduced IgM	2	5.9
Reduced IgG and IgA	1	2.9

Table-VI

Distribution of patients by flow cytometry (N=9)

Flow cytometry	Frequency (n)	Percentage
Normal	2	22.2
Severe combined immunodeficiency	6	66.7
X-linked agammaglobulinemia	1	11.1

Table-VII

Distribution of patients by flow cytometry (N=9)

Case no.	1	2	3	4	5	6	7	8	9
Lymphocyte	2286↓	4035	1488↓	2940↓	5042	2352↓	4392	2883↓	3410↓
CD3+CD4+(T)	983↓	974↓	640↓	1540	2246	1006↓	2152	1254↓	2319
CD3+CD8+(T)	960	931	348↓	850	1240	988	615	1124	546↓
CD19+(B)	222↓	2066	3↓	100↓	1226	71↓	1185	38↓	239↓
CD56+(NK)	74↓	64↓	400	450	210	188↓	290	389	232

Discussion

The present study observed that underlying diseases can be identified in 83.7% patients with persistent pneumonia. Saad K. et al[4] could identify underlying diseases of persistent pneumonia in 88.8% cases. Kumar M. et al[5] identified underlying diseases in 97.5% and Rahman S. et al[10] in 83.3% cases of persistent pneumonia. Hossain N. et al[7] could identify underlying diseases of recurrent and persistent pneumonia in 96.6% patients.

In present study, 13(26.5%) patients had cystic fibrosis. Hossain N. et al[7] found 4(13.3%) patients of cystic fibrosis and Rahman S. et al[10] found 1(4.2%) patient of cystic fibrosis among the cases with persistent pneumonia. However, it was more common among patients with recurrent pneumonia (19.7%).[10] The proportion of cystic fibrosis was higher in the present study as compared to others because of availability of sweat chloride test in Bangladesh Shishu Hospital & Institute now. Moreover, Bangladesh Shishu Hospital & Institute has the first ever established Pediatric Pulmonology Department with well set up. So, patients from all over Bangladesh are referred here.

Patients with congenital cardiac lesions causing left-to-right shunting and an increased pulmonary blood flow have an increased susceptibility to respiratory infections.[11] Echocardiography finding showed that 10(20.4%) patients have abnormal echocardiography. Among them, Atrial septal defect (ASD) and Ventricular septal defect (VSD) were common abnormalities. A review of literature revealed that congenital heart disease accounts for 4.9–16.6% of cases of persistent pneumonia.[4,5,7,10,12,13]

Children with immune defects usually present with highly recurrent and/or severe bacterial infections of the respiratory tract without any seasonality, recurrent gastrointestinal infections and recurrent skin infections. [4] In present study, 10(20.4%) patients were diagnosed as Primary Immunodeficiency- 6 patients of severe combined immunodeficiency (SCID), 1 patient of X-linked agammaglobulinemia and 3 patients of selective IgA deficiency. Saad et al found Immune deficiency disorder in 14.8% cases of persistent pneumonia. [4]Kumar M. et al[5] found Immunodeficiency in 7.3% cases of persistent pneumonia all of whom were HIV positive. Hossain N. et al identified 10% cases and Owayed AF et al[13] identified 10% cases with Immune deficiency disorder. Immunoglobulin replacement therapy reduced the frequency and severity of infections in hypogammaglobulinemia, although long-term pulmonary complications may occur.[7]

Gastro-oesophageal reflux disease (GERD) should be considered as a probable cause of persistent pneumonia when patient presents with vomiting or regurgitation of feed. In our study, we found 5(10.2%) cases of GERD diagnosed by contrast oesophagogram. All these patients had aspiration pneumonia in plain radiograph. Kumar M. et al[5] showed 12 (29.2%) patients had aspiration due to GERD among 41 patients of persistent pneumonia. Hossain N. et al[7] found 6.6% patients having Gastroesophageal reflux disease. Rahman S. et al[10] could identify 8.3% patients of persistent pneumonia having GERD.

The proportion of pulmonary tuberculosis was lower in the present study (8.2%) as compared to others because the treatment of pulmonary tuberculosis is available in all over Bangladesh. Therefore, patients usually do not come for the treatment of pulmonary tuberculosis in tertiary level hospital like Bangladesh Shishu Hospital & Institute. In the retrospective study done by Hossain N. et al, pulmonary tuberculosis was found in 23.3% patients.[7] Rahman S. found 12.5% patients having

pulmonary tuberculosis.[10] Kumar M. et al[5] found 19.2% and Saad K. et al[4] found 22.2% while Bolursaz MR et al[8] found 38.75% patients of persistent pneumonia having pulmonary tuberculosis evidenced by positive MT and gastric lavage GeneXpert.

Persistent chest infections are often the presenting feature of congenital abnormalities of the airways, lung parenchyma and pulmonary vasculature. One (2%) patient of the present study had congenital pulmonary airway malformation. Previous studies reported congenital anomalies of respiratory tract in 3.3-8% cases.[4,5,7,10,13] Therefore, such an abnormality should be suspected if one lobe is repeatedly infected or if there is incomplete resolution after treatment. [14]

No underlying disease could be identified in 8(16.3%) patients. Among them 3 patients had cerebral palsy having pharyngeal incoordination evidenced by difficulty in swallowing and drooling. 2 patients had pneumonia with resistant organisms, 2 patients developed lung abscess and 1 had fungal pneumonia.

The current results and a review of the literature reveal that the underlying diseases of persistent pneumonia in children from different geographical areas are similar, but with variable prevalence.[4,5,6,7,8,9,10,11]

Our study has certain limitations. The sample size was relatively small and a uniform set of investigations were not performed in all patients due to financial constraint. Bronchoscopy, genetic analysis for CFTR mutation and for primary immunodeficiency could not be done due to unavailability at the hospital.

Conclusion

In this study, underlying diseases could be identified in majority cases of persistent pneumonia. Common underlying diseases were cystic fibrosis, congenital heart disease and primary immunodeficiency followed by gastro-esophageal reflux disease, pulmonary tuberculosis and congenital anomalies of respiratory tract. Further studies can be undertaken by including large number of patients from different hospitals.

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Conflict of Interest

There is no conflict of interest regarding the research, authorship and publication of this article.

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