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ORIGINAL ARTICLE

Primary Immunodeficiency Disorders in Children Suffering from Persistent Pneumonia: Experience from A Tertiary Care Hospital

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Abstract

Background: *Persistent pneumonia in children poses a significant challenge to the pediatricians as there are underlying diseases.Primary immunodeficiency disorders (PID) are not uncommon among them. PIDs are always underdiagnosed and underreported from developing countries.*

Objective: *To identify the prevalence and varieties of PID among children with persistent pneumonia.*

Methods: *The crosssectional observational study was conducted atPICU (Paediatric Intensive Care Unit) of 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 the 49 cases, there were 10 (20.4%) cases of PID. Other underlying diseases were cystic fibrosis 13 (26.5%), congenital heart disease 10 (20.4%), gastro-esophageal reflux disease 5 (10.2%), pulmonary tuberculosis 4 (8.2%) and congenital anomaly of respiratory tract 1 (2%). Among the 10 cases of PID, there were 6 patients of SCID, 1 patient of X- linked agammaglobulinemia and 3 patients of selective IgA deficiency.*

Conclusion: *PID was the second most common cause of persistent pneumonia in our study. Among the PID, SCID was the commonest.*

Keywords: *Persistent pneumonia, primary immunodeficiency.*

Introduction

Pneumonia is the most common cause of morbidity and mortalityin 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 poses a significant challenge to the paediatricians and respiratory physicians[5] as there are underlying reasons of persistence. Primary immunodeficiency

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disorders are not uncommon among them. Primary immunodeficiency disorders are heterogenous group of inherited disorders that affect different components of immune system. PIDs are broadly classified as disorders of adaptive immunity (i.e., T cell, B-cell or combined immunodeficiencies) or of innate immunity (e.g., phagocyte and complement disorders). IgA deficiency is the most common PID, occurring in approximately 1 in 300 to 1 in 500 persons in United states.[6] Prevalence of other varieties is approximately 1 in 1200 live births.[6] PIDs are always underdiagnosed and underreported from developing countries. Although the clinical manifestations of PIDs are highly variable, many disorders manifest as an increased susceptibility to infection. Children with immune defects usually present with highly recurrent and/ or severe bacterial infections without any seasonality. PIDs should be suspected in patients with recurrent sinus or ear infections or pneumonias within a 1-year period, failure to thrive, poor response to prolonged use of antibiotics, persistent thrush or skin abscesses, or a family history of PID. The accurate and timely diagnosis of these disorders requires a high index of suspicion and specialized testing.[7] Recurrent and persistent pulmonary infections lead to chronic lung changes which increase morbidity and mortality. Early diagnosis and treatment are crucial for preventing significant disease-associated morbidity and improving patient outcomes.[8,9] It is important to note that PIDs are distinct from secondary immunodeficiencies that may result from other causes, such as viral or bacterial infections, malnutrition, immunoglobulin (Ig) loss, malignancy or immunosuppressive therapy.[10-12]

Materials and Methods

The cross-sectional observational study was conducted at PICU (Paediatric Intensive Care Unit) of 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 is defined as features of lower respiratory tract infection (i.e., cough, tachypnoea and fever with or without chest retractions) with radiological evidence of infiltrates or consolidation in the lungs persisting for 30 days or more, despite receiving antibiotics for a minimum period of 10 days.[5,13] Children who had history of prolonged mechanical ventilation during neonatal period, were taking immunosuppressive drugs or suffering from diseases causing immunosuppression 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 CXR, gastric lavage for AFB and gene Xpert, MantouxTest, echocardiography and HIV screening were done in all patients. S. 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 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 S. Immunoglobulins and/or T-cell, B-cell or NK-cell markers detected by flow cytometry were diagnosed as primary immunodeficiency. 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.

Results

A total of 52 cases of persistent pneumonia were initially enrolled. Three 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).

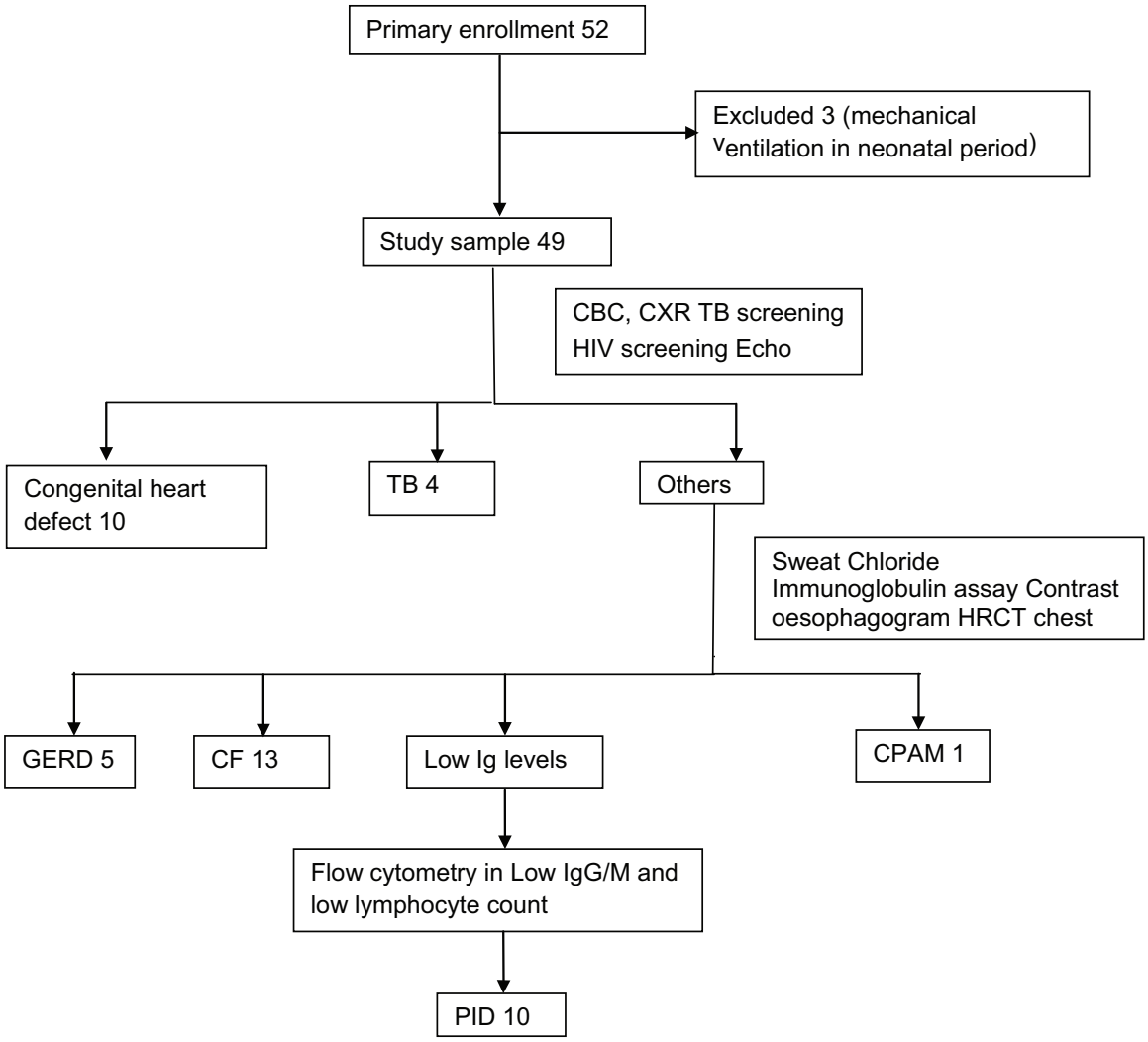

Fig.-1 *Flow diagram*

Table I
Distribution of patients by demographic status (n=49)

Socio- demographic status	Frequency	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
Consanguinity		
Absent	44	89.8
Present	5	10.2

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).

Primary immunodeficiency was diagnosed by interpreting serum immunoglobulin assay and flow cytometry. Serum immunoglobulin assay was performed in 34 patients. Twenty six (74.5%) of them had normal immunoglobulin levels. Reduced IgA was found in 3 (8.8%) patients while 2 (5.9%) patients had reduced IgG, 2 (5.9%) had reduced IgM and 1 (2.9%) had reduced IgG and IgA (Table III).

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 serum immunoglobulin assay (n=34)

Serum immunoglobulin assay	Frequency	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

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 IV, V). None of the patients were HIV positive.

Table IV
Distribution of PID 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

Other underlying diseases were cystic fibrosis 13 (26.5%), congenital heart disease 10 (20.4%), gastro-esophageal reflux disease 5 (10.2%), pulmonary tuberculosis 4 (8.2%)and congenital anomaly of respiratory tract 1 (2%). In 8 (16.3%) patients no cause could be identified.

Discussion

The present study observed that underlying diseases can be identified in 83.7% patients with persistent pneumonia. Ten (20.4%) patients were diagnosed as Primary Immunodeficiency- among them 6 patients were severe combined immunodeficiency (SCID), 1 patient had X-linked agammaglobulinemia and 3 patients were selective IgA deficiency. In a study in Egypt, Saad et al[4] could identify underlying diseases of persistent pneumonia in 88.8% cases. They found Immune deficiency disorder in 14.8% cases of

Table V
Flow cytometry reports 9 cases (n=9)

	Case number								
Variable	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

persistent pneumonia, all of them had hypogammaglobulinemia. Hossain et al[14] could identify underlying diseases of recurrent and persistent pneumonia in 96.6% patients. Among them, 10% hadimmune deficiency disorder who had hypogammaglobulinemia and recurrent pneumonia.

Owayed et al[15] identified underlying illness of persistent pneumonia in 87.8% patients, among them 10% (8 patients) had immune deficiency disorders. Five of them had ELISA positive for HIV and three children had selective IgA deficiency. In a Turkish study by Ozdemir et al[16], an underlying illness of recurrent pneumonia was identified in 90.3% patients. Among them, immune deficiency disorders were diagnosed in 17.75% (11 patients), common variable immunodeficiency in 5, combined immunodeficiency disease in 3, IgG and IgA deficiency in 2 and ataxia-telangiectasia in 1 patient. Bangladeshi study by Roy et al[17] showed 44% patients of persistent and recurrent pneumonia had PID. Among the PID, 38.3% had combined IgG and IgA deficiency, 23.1% had selective IgA deficiency, combined IgG, IgM and IgA deficiency in 15.4%, combined IgM and IgA deficiencyin 7.7%, isolated IgG deficiency in 7.7% and NK cell deficiency in 7.7% patients.

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] The ten warning signs for PID in children are - ≥4 new ear infections within 1 year, ≥2 serious sinus infections within 1 year, ≥2 months on antibiotics with little effect, ≥2 pneumonias within 1 year, failure to gain weight or grow normally, recurrent deep skin or organ abscesses, persistent thrush in mouth or fungal infection on skin, need for IV antibiotics to clear infections, ≥2 deep-seated infections including septicemia and a family history of PID.[18] Immune deficiencies should be suspected in children with infections that are especially severe and recurrent, that are caused by unusual organisms, or that involve multiple sites in addition to the lungs.[19,20]

Patients with SCID usually present within the first year of life with chronic diarrhoea and failure to thrive; severe and recurrent infections with opportunistic pathogens (e.g., Candida albicans, Pneumocystis jiroveci, or cytomegalovirus); and skin rashes. SCID is a paediatric emergency since severe infection often leads to death.[8,21]

B-cell (antibody-deficiency) disorders are the most common type of immunodeficiencies, accounting for approximately 50% of all PID diagnoses.[8] They comprise a heterogeneous group of disorders characterized by an increased susceptibility to respiratory tract infections with bacteria, particularly Streptococcus pneumoniae and Haemophilus infuenzae. Most common disorders in this category include: X-linked agammaglobulinemia (XLA, also known as Bruton's agammaglobulinemia), common variable immunodeficiency (CVID) and selective IgA deficiency. XLA is characterized by markedly reduced levels of circulating B-cells and serum IgG, IgA and IgM. Affected males usually present within the first 2 years of life with recurrent sinopulmonary infections and absent lymph nodes and tonsils.[8] CVID is a heterogeneous disorder characterized by markedly reduced serum concentrations of IgG, low levels of IgA and/or IgM, and poor or absent responses to immunization. Selective IgA deficiency is characterized by low or absent levels of serum IgA in the presence of normal levels of IgG and IgM. Most patients with IgA deficiency are asymptomatic. Among those that are symptomatic, up to one-third experience recurrent infections.[8]

Immunoglobulin replacementtherapy reduced the frequency and severity of infections in hypogammaglobulinemia, although long-term pulmonary complications may occur.[14]

Boyle et al[6] found population prevalence of diagnosed PID is 1 in 1,200 persons in the United States. Among them 35% CVID, 26% IgA deficiency, 13% Agammaglobulinemia, 9% SCID, 9% CGD, 9% IgG subclass deficiency in USA population.[6]

In an Egyptian study, predominantly antibody deficiencies were the most common category (35.9%) followed by combined T- and B-cell immuno-deficiencies (29.7%), other well defined immunodeficiency syndromes (18.7%), congenital defects of phagocyte number, function or both (12.5%) and diseases of immune dysregulation (3.1%).[22] In 80 children with primary immuno-deficiency syndromes in Tehran, the prevalence of antibody deficiencies, phagocytic defects and combined immunodeficiencies were 36.25%, 32.5% and 31.25% respectively.[23] Among these disorders, CVID

(13.75%) and SCID (12.5%) had the highest prevalence and the lowest prevalence were reported for cyclic neutropenia (5%), ataxia-telangiectasia (5%), and transient hypogammaglobulinemia of infancy (3.75%).[24] In the European Internet based patient and research database for primary immunodeficiencies with 2880 patients, CVID was the most common (21%) entity.[24] This was also true in a study conducted by Stray-Pederson et al. in Norway.[25] Our findings were not fully compatible with these studies, because our study is conducted in a tertiary center with a small number of patients presented here. Therefore, the prevalence of different PIDs cannot be generalized to the whole country. Moreover, patients admitted to PICU had critical acute illnesses or chronic difficult-to-treat complications. Thus, the study had only the severe complicated forms of PIDs. In our country, there is no study of PID on general population, nor any facility for newborn PID screening.

In our study, M:F ratio is 9:1. In other studies, the overall male predominance was 1.4 to 2.3 times than female.[22-24] This higher male predominance in our study was probably due to more social adherence to male child, therefore giving more care and privilege to male babies in the family.

The diagnosis of PID has been increased during the past decades. As noticed, an overall increase in incidence over time could be due to better diagnostic tools and increased awareness of physicians regarding these disorders. Such epidemiological data are needed to raise the awareness of the medical community about PIDs and to support the public health benefits of early diagnosis and treatment.

Our study has certain limitations. Thegenetic analysis for primary immunodeficiencycould not be performed which is crucial for the diagnosis of PID.

Conclusion

PIDs are not rare. In this study, PID was the second most common cause of persistent pneumonia in critically ill children. Among the PID, SCID was the commonest. Further studies including large number of patients from different hospitals should be performed.

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