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Clinical Profile of Primary Immunodeficiency Disorders: A Preliminary Report from a Tertiary Care Hospital in Bangladesh

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Abstract

Background: Primary immunodeficiency disorders (PIDs) or inborn errors of immunity (IEI) are inherited disorders that impair the immune response in children. PIDs are much more common than it was previously estimated. Unfortunately, the majority of these patients remain undiagnosed and untreated. **Objective:** To assess the demography, clinical profiles, and sub-types of PID cases. **Method:** It was a retrospective study conducted in the pediatric rheumatology division of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh from July 2012 to June 2020. All the diagnosed immune-deficient patients who fulfilled the inclusion criteria were included in this study. The PID patients were screened for CBC, serum immunoglobulin classes and subset of lymphocytes, including the T-B-NK cell markers, detected by flow cytometric analysis. **Result:** Among twenty-five PID cases included in this study, majority were antibody deficiency (40%) and combined immunodeficiency disorders (32%), followed by complement deficiencies, NK cell defect, and autoinflammatory disorders (CANDLE syndrome). Recurrent respiratory tract infection, ear infection, sinusitis and skin infection were the common clinical manifestations of this cohort. Late presentation and late diagnosis were found in almost every case. A comparison with PIDs reported from other countries showed that predominantly antibody deficiency cases were more common in those countries, but combined immunodeficiency was the most common (32%) sub-type in our country. **Conclusion:** Antibody deficiency and combined immune deficiency disorders were the predominant types of PIDs in this cohort. Late presentation and late diagnosis with different systemic infections in the disease course were observed.

Keywords

PIDs, IEI, Pediatric Age Group, Warning Signs

*Retired.

1. Introduction

Primary immunodeficiency disorders (PIDs) or inborn errors of immunity (IEI) are inherited disorders that impair immune response in children, leading to increased risk of infections, allergy, autoimmunity, auto-inflammatory disorders and malignancy. They are classified as "rare diseases," but their global incidence is more common than generally believed [1]. Most of the disorders start manifesting their clinical presentations in childhood, while milder forms may not be recognized until adulthood [2]. If all IEIs are considered, up to 1% of the global population may have a PID, which is much higher than previously predicted [3].

Around the world, more than 6 million people are affected by primary immunodeficiency disorders, among which 70% to 90% remain undiagnosed [3]. A report published in 2019 warns that, worldwide, approximately 1 in 10,000 people are affected by PIDs [4], a number which was underestimated due to missed diagnosis. The prevalence of PIDs varies greatly from country to country and is quite high in many countries [5]-[11].

The clinical presentations of PIDs are highly variable. Quite often, the first signs of PIDs are repeated, persistent, unusual and difficult to treat infections, and occurrence of adverse events after receiving a live vaccine [12]. In general, children with PIDs develop infections more frequently, severely, usually with atypical organisms and need hospitalization for having injectable antibiotics for a prolonged period [13]. Defective antibody production causes increased susceptibility to bacterial infections that typically involve the upper and lower respiratory tract (otitis, sinusitis and pneumonia). Additionally, it may also cause recurrent abscesses in the skin or other organs [14]. T cell disorders are present as combined T and B cell immunodeficiency with susceptibility to bacterial, viral and fungal pathogens. These PIDs are generally more severe than antibody deficiencies [15]. Patients with defects in phagocytic cells (number, function or both), may present with recurrent and severe infections of fungal and bacterial origin. Respiratory tract, cutaneous infections and deep-seated abscesses are common infections in this type of PID. Complement disorders represent the rarest form of PIDs, accounting for only 2% and are usually recognized by recurrent infections caused by encapsulated bacteria [16].

Preventing infection in PID patients includes antimicrobial agents, immunotherapy, and immunization. The prophylactic measures might be as follows: antibiotic and antifungal prophylaxis for innate immune deficiencies; cotrimoxazole for cellular immune deficiencies; polyvalent immunoglobulin replacement therapy for humoral immune deficiencies; and vaccinations and antibiotic prophylaxis for patients with asplenia or complement deficiencies [17].

Noninfectious characteristics are other essential manifestations of PIDs that can result from inappropriate immune functions. These may include autoimmunity, malignancy, allergy, auto-inflammatory conditions and skeletal dysplasia. Due to deficient and deregulated immunity, some affected individuals present with autoimmune disease as the sole manifestation of PIDs [18].

Laboratory investigation includes the assessment of antibody and cellular response, as well as evaluation of the phagocytic and complement system. Flow cytometry and genetic assays generally served as confirmation tools to validate a diagnosis. The recent exponential increase in genetic analysis has facilitated the identification of known and novel mutations [18].

PIDs were initially thought to be a very rare condition in Bangladesh. However, as per the working experience of pediatric rheumatology division of Bangabandhu Sheikh Mujib Medical University (BSMMU), it is found that, PIDs are much more common than previously estimated, and till now, a majority of these patients continue to remain undiagnosed and untreated in our settings. There is a paucity of published literature on the PIDs in Bangladesh. The purpose of this study is to provide a baseline report from a tertiary care hospital on PIDs, highlighting the frequency, clinical profiles, and subtypes of different PID cases.

2. Methods

It was a retrospective study carried out in the Pediatric rheumatology division of the Department of Pediatrics, BSMMU, Dhaka, Bangladesh. All the diagnosed PID patients attending the outpatient or admitted to the inpatient department were enrolled in this study from July 2012 to June 2020. Initially suspicion was based on ten warning signs of PIDs, according to the Jeffrey Modell Foundation [11]. Any patient who fulfilled two or more of the 10 signs was defined as a suspected case of PID. Later on, the diagnosis was confirmed by doing a complete blood count, lymphocyte subset analysis by flow cytometry and estimation of serum immunoglobulin levels. Diagnosed PID cases from the medical records/computerized database documented in the pediatric rheumatology and immunology clinic of pediatric rheumatology division of BSMMU, were considered as cases in this report. Children with diabetes mellitus, cystic fibrosis or any other chronic illness, children getting cancer chemotherapy, prolonged corticosteroids or other immunosuppressive therapy, chronic/severe malnutrition and HIV infected children were excluded from the study.

Information on the PID patients was recorded in a pre-designed questionnaire. Patients' demographic information, past medical history including first clinical presentation, age of onset, history of consanguineous marriage of parents, family history of immunodeficiency, recurrent infections, autoimmune diseases and malignancies were documented. Clinical examination findings, including anthropometry were also obtained from the records. Immunoglobulin assay was done by an automated nephelometry analyzer. The value of IgG, IgA, IgE and IgM were compared with age-specific cut-off values established for children residing in Bangladesh [19]. Flow cytometric analysis was done for lymphocyte subset analysis to see the Gated cells (CD45+), T-cell markers (CD3+, CD3+CD4+, CD3+CD8+), B cell markers (CD19+) and NK cell markers (CD56+). Both the absolute values and values as percentages were plotted and compared with age-specific value chart [20]. Serum immunoglobulin assay and flow cytometry were analyzed in the Department of Microbiology and Immunology, BSMMU. Dihydro Rhodamine assay,

Nitroblue Tetrazolium test and genetic tests were not available in our settings before 2021, so, these tests were not done for the PID cases in this cohort. All clinical and laboratory information was collected, compiled and analyzed manually and presented in tabulated forms.

3. Results

The majority of the PID cases in this series were predominantly antibody deficiency cases (40%), followed by, combined immunodeficiencies (32%), complement deficiencies, NK cell defect cases, phagocytic defects and autoinflammatory disorder (CANDLE syndrome). Among the antibody deficiency disorders, there were 2 (20%) agammaglobulinemia, 2 (20%) XLA, and 2 (20%) common variable Immunodeficiency (CVID) cases. In the combined immunodeficiency group, there were 3 (37.5%) cases of Wiskott Aldrich Syndrome, 2 (25%) cases of ataxia telangiectasia, 2 (25%) cases of severe combined immunodeficiency disorder (SCID) and 1 (12.5%) hyper IgE syndrome (HIES) case.

The complement deficiency group had only one (4%) case of congenital C3 deficiency. In this preliminary report, we also had 3 (12%) NK cell defect cases, 1 (4%) severe congenital neutropenia, and 1 case of cyclic neutropenia (Table 1). Diagnostic delay was found from 8.5 months to 5.6 years in this cohort (Table 1).

Table 1. General characteristics of patients with primary immunodeficiency disorders (n = 25).

Types	Gender ratio (M:F)	Age at onset (years) Mean ± SD	Age at diagnosis (years) Mean ± SD	Delay in Diagnosis (years) Mean ± SD
Predominantly Antibody Deficiencies (n = 10, 40%)				
CVID (2)	0:2	3.6 ± 1.2	6.8 ± 2.3	3.9 ± 1.8
XLA (2)	2:0	3.4 ± 0.4	8.4 ± 4.7	5.6 ± 3.2
AR Agammaglobulinaemia (2)	1:1	2.1 ± 0.9	5.6 ± 3.1	3.5 ± 2.4
Transient Hypergammaglobulinemia of Infancy (2)	0:2	5.5 ± 1.3	6.9	1.4 ± 0.5
Hyper IgM syndrome (1)	M	5	7	2
Selective IgA Deficiency (1)	M	6	10	4
Combined Immunodeficiencies (n = 8, 32%)				
Wiskott Aldrich Syndrome (3)	3:0	7.0 ± 1.3	8.4 ± 2.6	1.4 ± 0.7
SCID (2)	2:0	0.6 ± 0.2	1.2 ± 0.3	0.7 ± 0.2
Ataxia Telangiectasia (2)	0:2	3.6 ± 0.9	4.6 ± 1.0	1.1 ± 0.3
JOB syndrome (1)	F	2.4	4	1.6
Complement Deficiencies (n = 1, 4%)				
Congenital C3 Deficiency (1)	F	6	6	2
Congenital Defect of Phagocyte Number and Function (n = 2, 8%)				
Severe Congenital Neutropenia (1)	M	8	12.5	4.5
Cyclic Neutropenia (1)	F	4	5.5	1.5
Others (n = 4, 16%)				
NK cell defect (3)	1:2	2.5 ± 1.4	4.7 ± 1.3	2.6 ± 1.1
CANDLE syndrome (1)	F	5	8	3

Age of onset was early in SCID (0.6 years) and agammaglobulinemia (2.1 years) cases, whereas late in severe congenital neutropenia (8 years) and Wiskott Aldrich Syndrome (7 years) cases. However, delay in diagnosis was highest in X linked agammaglobulinemia cases (5.6 years), and lowest in ataxia telangiectasia (1.1 year) cases (Table 1).

Table 2. Clinical manifestation of patients with primary immunodeficiency disorders (N = 25).

Variables	RTI	GIT infections	Ear infection	Sinus infection	Skin infection	UTI	Septic Arthritis	Meningitis
Predominantly Antibody deficiencies								
CVID (2)	√	√	√	√	√	√	-	-
XLA (2)	√	√	√	√	√	√	-	√
Agammaglobulinemia (2)	√	√	√	√	√	√	√	-
Transient Hypergammaglobulinemia of Infancy (2)	√	-	-	-	√	-	-	-
Hyper IgM syndrome (1)	√	-	√	√	-	-	-	-
Selective IgA Deficiency (1)	√	√	√	√	-	-	-	-
Combined Immunodeficiencies								
Wiskott Aldrich Syndrome (3)	-	√	-	-	√	-	-	-
SCID (2)	√	√	√	√	√	√	-	-
Ataxia Telangiectasia (2)	-	-	-	-	-	-	-	-
JOB syndrome (1)	√	-	-	-	√	-	-	-
Complement deficiencies								
Congenital C3 Deficiency (1)	√	-	-	-	√	√	-	-
Congenital defect of phagocyte number or function								
Severe Congenital Neutropenia (1)	√	√	√	-	√	-	-	-
Cyclic Neutropenia (1)	√	-	-	-	√	-	-	-
Others								
NK cell defect (3)	√	√	√	-	√	√	-	-
CANDLE syndrome (1)	√	√	-	-	√	√	-	-

Different clinical manifestations of the PID cases are shown in Table 2. Most antibody deficiency disorder patients experienced frequent respiratory tract infections, gastroenteritis, ear infection and skin infection. One CVID patient developed bronchiectasis and hearing impairment due to chronic supportive ear infection. Among combined immunodeficiency disorders, SCID patients were presented with recurrent pneumonia, diarrhea, urinary tract infection, sinusitis, and ear and skin infections. The only HIES patient presented with eczema, recurrent staphylococcal skin abscesses, recurrent lung infections, eosinophilia and high serum levels of IgE. Ataxia telangiectasia patients had frequent symptoms of respiratory tract infection, generalized weakness and difficulty in walking. Severe

congenital neutropenia (SCN) patient presented with recurrent pneumonia, one episode of thigh abscesses and septicemia with several episodes of otitis media and gastro-enteritis. There was one patient with cyclic neutropenia suffering from recurrent respiratory tract infection and skin infections in different sites of the body. Congenital C3 deficiency case had several episodes of pneumonia, urinary tract infection, skin abscess and gastroenteritis since her early childhood. She had a skin rash along with pain in multiple large and small joints. One X linked agammaglobulinemia patient developed meningitis, and one female child with agammaglobulinemia presented with septic arthritis (Table 2).

In Table 3, a comparison is shown among PID cases in different countries. The highest number of PID cases were reported in the USA (5484 cases, over a period of 28 years), followed by France (3083 cases over a period of 4 years). The present study could only document 25 PID cases in 8 years from a tertiary care hospital in Bangladesh (Table 3).

Table 3. Comparison of primary immunodeficiency disorders among various countries or regions [36].

Country or Region	Bangladesh (2012-2020)	India (2015-2019)	Malaysia (1979-2020)	Singapore (1990-2000)	Korea (2001-2005)	Taiwan Region (1985-2004)	French (2005-2009)	Brazil (1978-2011)	Kuwait (2004-2018)	USA (1992-2020)
No of cases	25	229	119	39	152	37	3083	1008	314	5484
Consanguinity	3.7%	Not Reported	2.5%	Not reported	Not reported	0%	15%	Not reported	78%	Not reported
Immunodeficiencies affecting Cellular and Humoral immunity	32.0%	11.3%	30.3%	10.3%	13.2%	11%	17.2%	6.7%	31.8%	9.6%
Combined Immunodeficiencies with associated Syndromic features	-	13.9%	17.6%	12.8%	-	-	14%	8.3%	21.7%	20%
Predominantly Antibody deficiencies	40.0%	20.6%	20.2%	41%	53.3%	46%	42.8%	60.8%	17.8%	49.2%
Disease of Immune Dysregulation	-	20.6%	10.9%	-	-	-	6.6%	5.3%	15%	4.2%
Complement deficiencies	4.0%	2.1%	-	-	-	-	0.5%	2.9%	7%	0.5%
Congenital defect of phagocyte number or function	08 %	10.9%	16.8%	15.4%	28.9%	24%	18.6%	8.7%	6.4%	12%
Autoinflammatory Syndrome	-		0.8%	-	-	-	-	1.3%	0.3%	-
Defects of Innate Immunity	-	20.6%	3.4%	-	-	-	0.2%	5.9%	-	-
Others	16.0%	-	-	17.9%	-	-	-	-	-	2.2%

The highest number of consanguinities was found in Kuwait (78%), followed by France (15%), whereas in Taiwan region it was 0%. In the present study, consanguinity was present in 3.7% of cases. Patterns of specific types of immunodeficiency disorders varied from place to place. Predominantly antibody deficiency cases were the most common (40%) sub-type found in Bangladesh, which was similar to studies from Brazil, Korea, the USA and Taiwan region where predominantly antibody deficiency cases were (60.8%, 53.3%, 49.2% and 46% respectively).

An Indian study found the highest number of antibody deficiencies and cases of immune dysregulation (20.6% each). Phagocytic defects (28.9%) were most common among Korean nationals (**Table 3**).

4. Discussion

PIDs are a group of hereditary diseases resulting in impaired development and function of the immune system. As a result, recurrent and serious episodes of bacterial, viral, protozoal and fungal infections take place and impair the affected patients to lead a normal healthy life [3]. Diagnosis of PIDs in Bangladesh is still a great challenge. Delayed diagnosis and late presentations are common, resulting in poor clinical outcome. Underdiagnosis might be very common in Bangladesh, as there is no population-based screening process for PIDs in our country. The present study was a tertiary care hospital-based retrospective cohort aiming at providing a baseline reference, which would help future studies to compare the demographic and clinical profiles of PID patients.

In the present study, the most common PIDs were predominantly antibody deficiencies combined with immunodeficiency (**Table 1**). A retrospective study from a tertiary care center in China on 112 PID cases reported a similar picture, where combined immunodeficiency was the majority (28.6%) followed by predominantly antibody deficiencies [21]. The Chinese study also found that, 17.8% of the patients had a family history of PIDs [21], which was not found in the present study.

Regarding individual PIDS, agammaglobulinemias (4 cases, 2 agammaglobulinemias, 2 XLA) were the most common disorders, followed by NK cell defect and WAS (3 cases each). SCID constituted 4% of PIDs in this study, which was higher than the study by Agha Mohammadi *et al.* from Iran but lower than the study by Noh LM *et al.* from Malaysia. SCID was present in 2.4% and 9.6% respectively [22] [23]. In the present study, there was a single case of cyclic neutropenia, and a case of CANDLE syndrome (**Table 1**). If we compare our results with a study in the same geographical area from India, the findings were different and showed combined immunodeficiency and phagocytic defects as common (equally in 29% of patients), followed by antibody deficiency (18%), defects in innate immunity and immune dysregulation [24]. Silva *et al.* from Sri Lanka, in their series, reported that 60.27% of PID cases had antibody deficiency [25]. In Mexico, the number of antibody deficiency cases was predominantly 65.3%. A few cases of complement deficiencies, congenital defects of phagocytes (number and function) and NK cell defects were also found in their cohort [26]. Thus, the prevalence and sub-types of PIDs vary from country to country depending on many socio-demographic factors and ethnicity. According to epidemiological studies, wide variations exist in the frequency of different types of PIDs, which may be influenced by geographical and racial factors [27]. Therefore, regional data regarding the prevalence of various types of PIDs can work as a powerful tool in improving the local healthcare system strategies and quality of care of patients diagnosed with PIDs.

However, the present report is from a very small cohort and a single center. So, no strong conclusion can be drawn.

In the present study, the mean age of diagnosis ranged from 1.2 to 12.5 years, depending on PID variants, with a mean diagnostic lag ranging from 0.7 to 5.6 years (**Table 1**). A study conducted by Reda SM *et al.* also showed a wide range of age at diagnosis (2 to 108 months) with a diagnostic lag up to 72 months. The findings were almost similar to the present study [28]. The delay in diagnosis might be due to a lack of awareness, resulting in non-suspicion of PIDs among healthcare personnel. Female patients are slightly more in our cohort, whereas males were more in registries of Sweden, Australia, and Kuwait [29]-[31]. This difference could also be explained by the small sample size of the present report, which led to a sample bias.

Repeated infections, especially infection of the respiratory tract (88%) and skin (84%), were the main features of PIDs in our settings (**Table 2**). Large sample cohort studies on PIDs reported that almost all PID cases had a history of recurrent infection before diagnosis [29]-[31]. Respiratory disorders are significant causes of morbidity and the leading causes of death (30% - 65%) in both children and adults with PIDs [32]. The most common clinical manifestations are infections involving the respiratory tract, e.g. rhino-sinusitis, otitis media, bronchitis, bronchiectasis and recurrent pneumonia (30% - 65%). Recurrent respiratory infections are often the first warning sign [33]-[35]. Gastrointestinal disorders and failure to thrive were also frequent in patients in this study. Recurrent gastrointestinal symptoms could be the first presentation of PID. One case of agammaglobulinemia presented with deep-seated infection in the form of septic arthritis. Aseptic arthritis is much more frequent than septic arthritis in secondary immunodeficiency like HIV infected patients [36].

The highest number of PID cases was reported from the USA. Patterns of specific types of immunodeficiency disorders vary from country to country. However, most of the country's data shows predominantly antibody deficiency cases as the most common sub-type, which is similar to our findings (**Table 3**).

Consanguineous marriage among parents was lower in Bangladesh compared with other South Asian and Middle East countries. A previous Bangladeshi study carried out with the aim to assess the prevalence, socio-demographic factors, reproductive consequences, and heritable disease burdens associated with consanguinity (CM) in Bangladesh identified the prevalence of consanguineous marriage as 6.64% [37]. In the present study, consanguinity was present among 3.7% of parents of PID cases. On the contrary, consanguinity was 78% in the Kuwait study (**Table 3**). There could be variable prevalence of consanguineous marriages in some areas responsible for different types and presentations of PIDs in different countries. High rates of consanguinity and familial cases were found in 25% of combined immunodeficiency in Swedish children and 31.2% of all PID patients in Australia [38] [39]. The high consanguinity in the Middle East increases the risk of genetic diseases, including PIDs. A retrospective analysis from Qatar during

1998-2012 found a positive family history of PID in 66.4% of cases and consanguinity in 61.1% of cases. Paternal parallel cousin marriages are the most common type of consanguinity. So, from a practicing physician's point of view, taking detailed family history is very important when suspecting PIDs in children [40].

An Indian study done in 2021 found defects in intrinsic and innate immunity in 20.6%, antibody deficiencies in 20.6%, and diseases of immune deregulation in 20.6% PID cases. In their study, auto-inflammatory disorders (2.1%) and complement deficiencies (1.0%) were the least common. Because they have done genetic testing in all their cases, they were also able to identify some rare cases of PIDs [41].

The frequency and types of PIDs found in this preliminary report may not reflect our country's actual scenario. There are limited laboratory facilities in the country, including dihydro rhodamine assay, nitroblue tetrazolium test, genetic analysis, etc. Additionally, late presentation and delayed referral with severe infections and complications were the important problems in our settings. Lack of knowledge and awareness, as well as poor referrals from physicians, might be other limitations. A high index of suspicion is necessary to diagnose immunodeficiency disorders in pediatric patients, as early diagnosis and treatment are crucial to minimize morbidity and mortality.

5. Conclusion

Recurrent infection is a common presenting symptom in most of the PID cases. Antibody deficiency and combined immune deficiency disorders were the predominant types of PIDs in this cohort. Delayed presentation and late diagnosis with different systemic infections in their disease course were observed. Inadequate laboratory support, including genetic analysis, was an important limitation in this study.

6. Recommendation

It is essential to create mass awareness, as the disease is still unknown to the general population and healthcare professionals. The true incidence and prevalence of PIDs will never be known until there is an arrangement of programs for newborn and population screening. International support is needed for low-income countries to provide diagnostics logistics, including genetic studies and treatment, as well as necessary medication and intravenous immunoglobulins (IVIG).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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