RESEARCH PAPER

# Diagnostic Spectrum and Clinical Profile of Primary Immunodeficiency Disorders at a Tertiary Care Children Hospital in Southern India

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**Background:** Primary immunodeficiency disorders are genetically heterogeneous immune disorders with a wide range of infectious and non-infectious manifestations. **Objective:** To describe a single-center experience of primary immunodeficiency disorders. **Design:** Retrospective analysis from January 2015 to January 2020. **Setting:** Tertiary care children's hospital. **Participants:** One hundred and twelve children (<18 years) diagnosed with primary immunodeficiency disorders. **Outcome measure:** Diagnostic spectrum, clinical features, and outcome. **Results:** The median (IQR) age of the first clinical manifestation and lag time in diagnosis was 10 (27) and 11 (18) months, respectively. Twenty-seven children (24%) were diagnosed during their first presentation. Thirty-six (32%) children had phagocytic disorders, 20 (17.8%) had combined/cellular defects, 18 (16%) had predominant antibody deficiencies and 17 (15%) had disorders of immune dysregulation. Non-infectious manifestations were seen in 54 (48%). Eight children underwent hematopoietic stem cell transplantation, 44 (39%) children were on antimicrobial prophylaxis and supportive therapy, 36 (32%) were lost to follow-up and 24 (21%) children died. **Conclusion:** Congenital defects of phagocyte function, followed by combined/cellular defects are the commonest primary immune deficiencies (PIDs) identified in southern India. Long lag time in diagnosis and high mortality in our cohort emphasizes the need for early diagnosis and early referral.

**Keywords:** *Hematopoietic Stem Cell Transplantation, Phagocytic disorders, Primary Immunodeficiency, Recurrent infections, Severe Combined Immunodeficiency*.

Primary immune deficiencies (PIDs) are a group of heterogeneous immune disorders that affect distinct components of the adaptive and innate immune system. The clinical presentation is variable and includes increased susceptibility to infections, autoimmunity, auto-inflammatory diseases, allergy, and/or malignancy. It can present in the neonatal period or as late as adulthood depending upon the severity of the immune defect [1].

With the ongoing discovery of novel mutations, the numbers of genetically defined PIDs are currently estimated to be more than 400 [2]. The prevalence of PIDs may be as high as 1:1200 as reported from the United States [3]. So far, there is no nationwide data on the prevalence of PIDs in India which is expected is expected to be higher than the US due to a higher rate of consanguineous marriages. Based on statistical projections it is estimated that there could be more than one million patients with PIDs in India [4]. While awareness for PIDs is increasing, with advances in diagnosis and management, they continue to remain under-diagnosed and under-treated [3,5]. The reasons for a high drop-out rate on follow-up are probably lack of understanding of disease, denial of diagnosis, and the costs involved in the treatment and follow-up. This could be improved by establishment of patient support groups with advice, education, and support to families.

We describe the clinical spectrum and outcome of PIDs over the last 5 years in children at a tertiary care hospital from South India.

## METHODS

A retrospective analysis of case records of children (<18 years) diagnosed to have PIDs from January 2015 to January 2020 at Kanchi Kamakoti Childs Trust Hospital, Chennai was performed. PIDs were classified according to the International Union of Immunological Societies (IUIS 2017) classification [6]. Children with immune deficiencies secondary to HIV infection, chemotherapy, or chronic steroid therapy were excluded from the study. This study was approved by the institutional ethics committee.

The details collected were age at the onset of symptoms, type of clinical presentation, time of diagnosis, family history of illnesses or PID, laboratory findings, microbiological data, confirmatory diagnosis, treatment and outcome. The diagnosis of PID was confirmed based on characteristic clinical presentation, relevant laboratory data, and gene analysis. Laboratory investigations included complete blood count, peripheral smear, and relevant immunological workup. Immunoglobulin profile, nitroblue tetrazolium test, flow cytometry based analysis of peripheral blood lymphocyte subset and dihydrorhodamine assay, Bruton tyrosine kinase (BTK) expression, CD11b/18 expression, CD107a/perforin assay, Wiskott-Aldrich Syndrome Protein (WASP) expression, Dedicator Of Cytokinesis 8 (DOCK 8) expression and IFNα/IL12RB expression were done based on the clinical suspicion. Bone marrow aspiration was performed in the presence of prolonged fever, cytopenia and features of hemophagocytic lymphohistiocytosis. Flow cytometry based tests were performed at the National Institute of Immuno-Hematology, Mumbai. Next-generation sequencing based genetic test was performed at MedGenome Labs Ltd, Bangalore. Genetic testing could not be performed in all children due to cost constraints.

## RESULTS

During the study period, 112 children (65 boys, 47 girls) were diagnosed with PIDs. Most of the children (*n*=69) belonged to the state of Tamil Nadu followed by Andhra Pradesh (*n*=38, 34%).

The diagnostic spectrum and clinical profile are depicted in **Fig. 1** and **Supplementary Table I**. Molecular diagnosis was performed in 42 (37.5%) children. Sixty-five (58%) children had weight less than the 3rd centile. Positive family history was noted in 32 (28%) children, with a history of sibling death in 26 (24%) cases. Parents of 64 (58%) children had consanguineous marriage. The predominant mode of inheritance observed was autosomal recessive (*n*=28, 66%).

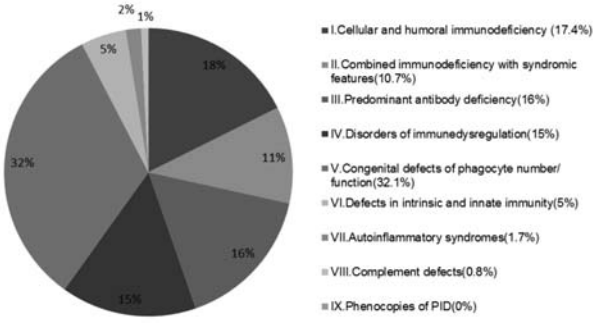


**Fig.1** Diagnostic spectrum of primary immunodeficiency disorders at a pediatric tertiary care center, 2015-2020 (*N*=112).

The median (IQR) age at onset of first clinical manifestation was 10 (27) months (range 0-12 years) and it varied depending on the underlying PID (**Supplementary Table 1)**. The median (IQR) age at diagnosis was 18 (17) months (range 0 -15 years) with median (IQR) lag time in diagnoses as 11(18) months (range 0-12 years). Twenty-seven (24%) children were diagnosed during their first presentation. The most common presentation recurrent/persistent pneumonia (*n*=39, 34%), followed by recurrent/persistent diarrhea (*n*=21, 18.5%). Non-infectious manifestations were seen in 54 (48%) children and were the main presenting symptom in 24 (21%) children, atopy being the commonest (*n*=11) presentation. Microorganisms were identified on 48 occasions in our cohort.

Forty-four (39%) children remain on supportive therapy such as immunoglobulin replacement, antimicrobial prophylaxis, and/or specific therapy. Children with autoimmune manifestations received immunosuppressive agents. One child with LRBA defect with refractory autoimmune cytopenia was started on abatacept (cytotoxic T-lymphocyte associated 4-immunoglobulin fusion protein) therapy and sirolimus after which his hemoglobin and platelet count stabilized.

Eight (7%) children underwent hematopoietic stem cell transplantation (2-CGD, 1-WAS, 1-LRBA, 1-Familial HLH, 2-DOCK8, 1-MSMD), of whom 7 children are in remission with a durable graft. One child with MSMD had a graft rejection and received anti-tuberculous therapy. Thirty-six (32%) children were lost to follow up. Twenty-four (21%) children died with the cause of mortality as severe infection (*n*=13), refractory HLH (*n*=8), refractory immune cytopenia with intracranial bleeding (*n*=2), and lymphoma (*n*=1).

## DISCUSSION

The most common PIDs observed in our study were congenital defects of phagocyte number or function followed by combined/cellular defects.

Our study had some limitations as we received children with critical acute illnesses or difficult to treat chronic conditions, which may have led to only severe forms of PIDs being recognized. The response to polypeptide vaccines was not assessed. Children were referred from southern regions of India, limiting geographical generalizability of the study findings. Detailed analysis of ethnicity, race and religion was not carried out limiting comparison to earlier Indian studies.

While, in earlier reports from India, antibody deficiencies were predominantly described from Chandigarh (42%) [4], disorder of immune dysregulation from Mumbai (33.8%) [7], and combined cellular and humoral immunodeficiency (29%) and phagocytic defect (29%) from Delhi [8]. In most parts of the world, antibody deficiency disorders are the most common PIDs reported [9,10]. The variance observed in our population could be due to genetic and racial factors with a high frequency of consanguineous marriages. Mild PIDs such as isolated immunoglobulin deficiencies may be under-diagnosed in our country [11]. The collection of pooled data from other centers in India through registries would be vital for this.

The ten warning signs of PIDs help in early recognition but do not cover the expanding spectra of non-infectious manifestations [12]. In our cohort, a high proportion of children had non-infectious manifestations, which were also the presenting symptoms similar to earlier reports [13,14].

The International Union of Immunological Society proposed a recent phenotypic and genotypic classification of PIDs [15]. A subset of patients (LRBA, DOCK8, and IL2RA defect) in our series was diagnosed based on genetic analysis. Next-generation sequencing (NGS) offers diagnostics and development of novel targeted therapies in cases where primary investigations are inconclusive [16,17].

Interventions in the form of early hematopoietic stem cell transplantation (HSCT), before the onset of serious infections, have improved 5-year survival to >90% [18,19]. Eight children underwent curative HSCT in this study. More than 100 transplants have been carried out so far in 10 centers across the country and more than half are doing well [20,21]. Barriers to cure include lack of early diagnosis and referral, lack of awareness on management of PID including HSCT and the prohibitive costs.

The high mortality of patients with SCID in our study demonstrates the need for awareness and implementation of newborn screening for SCID in the near future. The implementation of universal newborn screening (TREC – T cell receptor excision circle assay) would help in early diagnosis and timely access to treatment in these children [21].

The Indian Society for Primary Immune Deficiency (ISPID), initiated in 2011, is working towards increasing the awareness of PIDs, the establishment of diagnostic support and research centers, and also towards the development of a national PID registry. With such an initiative, there is scope for improving the outcome for children affected with PID [23].

Congenital defects of phagocyte function followed by combined/cellular defects were the commonest disorders. A consistent algorithm and a high index of suspicion will go a long way in improving early diagnosis and appropriate management of PIDs. Further modifications to include other early warning signs in the light of the growing spectra of PIDs are essential to ensure early identification.

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## CLIPPINGS

**Standard deviation scores of 17-OHP and other analytes in classical CAH** *(Horm Res Paediatr 2020;93:226-38)*

The management of congenital adrenal hyperplasia is guided by clinical assessment and measurement of biochemical parameters, chiefly 17-hydroxyprogesterone (17-OHP) and androgen metabolites. However, a single cutoff value of these analytes is difficult to define, and levels may vary with age, phenotypes and between different laboratories and assay methods. This study measured and expressed the SD scores of levels of 17-OHP, androstenedione, dehydroepiandrosterone-sulphate (DHEAS), and testosterone using liquid chromatography-tandem mass spectrometry in 38 children (aged 3-18 years) diagnosed with classical CAH. The biohemeical profile was corroborated with the clinical outcomes. The majority (86%) of the patients had elevated 17-OHP levels while consuming hydrocortisone in replacement dose of 12.6 $mg/m^2$/day. The levels of androstenedione were within ±2 SD but DHEAS levels were below -2SD. The authors reiterated the need to develop gender- and age-specific cutoffs while interpreting these hormonal levels for optimum titration of dose of replacement steroids.

**Kisspeptin levels in prepubertal obese and overweight children** *(Eur Rev Med Pharmacol Sci. 2021; 25:941-49).*

Kisspeptin is an important neuropeptide involved in regulation of the hypothalamo-gonadal axis. The concentrations of this neuropoetide were measured using radioimmunoassay in 54 prepubertal children (22 boys) who were overweight or obese and compared with 25 normal weight prepubertal children. The metabolic (glucose and insulin levels after oral glucose load, total- LDL- HDL-cholesterol, triglycerides, uric acid), hormonal (fT3, fT4, TSH, IGF-1, leptin) and total antioxidative capacity were also measured and correlated. The levels of kisspeptin were found similar in obese and normal-weight children but were lower in obese males than females. Kisspeptin did not correlate with BMI, HOMA-IR, Insulin peak levels and total antoxidative capacity; however, it significantly correlated with fT3 levels. Leptin levels were higher in obese children and positively correlated with total antioxidative capacity. The authors concluded further studies to understand this complex central regulation and interaction with oxidative stress in children.

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