Original Article

Spectrum of Primary Immune Deficiency at a Tertiary Care Hospital

Sumit Verma, Pradeep Kumar Sharma, Sindhu Sivanandan, Nidhi Rana, Savita Saini, Rakesh Lodha and S.K. Kabra

Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India

ABSTRACT

Objective. To report various primary immune deficiencies diagnosed in children at a tertiary care hospital, their clinical manifestations and laboratory profile.

Methods. Case records of children diagnosed to have primary immunodeficiency disorders over a period of 24 months at a tertiary care hospital in northern India were evaluated.

Results. Twenty-seven children (M: F=3.5: 1) with mean age of 5.4 ± 4.6 yrs (2mo-16yr) were diagnosed to have primary immunodeficiency. Thirteen children had chronic granulomatous disease (CGD), 4 had severe combined immunodeficiency (SCID), 4 had hypogammaglobulinemia, 2 had Ataxia telangiectasia, and one each had DiGeorge syndrome, Wiskott Aldrich syndrome, hyper IgM syndrome and leukocyte adhesion defect. Common mode of presentation were recurrent/ persistent pneumonia in 19, recurrent/ persistent diarrhea in 10, deep seated abscesses in 8, allergy in 3, disseminated tuberculosis infection in 2, extensive fungal infections in 2 and 1 each of disseminated cytomegalovirus (CMV) infection, disseminated BCG disease, otitis media and meningitis. Family history of sibling deaths was elicited in 2 families. Infectious agents were isolated in 16 cases.

Conclusion. From a single center 27 patients with primary immune deficiency could be identified by chart review, suggesting need for high index of suspicion for diagnosis of primary immune deficiency in India. Though the exact prevalence is not known there is need to make a registry to document the magnitude of problem of these disorders. **[Indian J Pediatr 2008; 75 (2) : 143-148]** *E-mail: skkabra@rediffmail.com, skkabra@hotmail.com*

Key words: *Chronic granulomatous disease; Panhypogammaglobulinemia; Primary immune deficiency; Severe combined immune deficiency*

Immunity plays a vital role in prevention and control of infections during childhood. Immunodeficiency disorders either inherited (primary) or acquired (secondary), increase susceptibility to infections. In recent times, the human immunodeficiency virus (HIV) epidemic and the consequent opportunistic infections has led to recognition of acquired immunodeficiency disorders. However, the inherited or primary immunodeficiency diseases are still under-diagnosed entities. Relatively uncommon, these illnesses are easily missed in a child with "too many" infections and poor response to conventional treatment. In India, the literature on these diseases is limited to case reports.[1-3] This suggests that majority of infants may be dying due to infections without diagnosis. The reason for missing the diagnosis may be many and include: low index of suspicion, very high rates of infections in the general population and non-availability of diagnostic facilities at most centers. Since there is no central registry for immune deficiency disorders, whatever numbers are diagnosed are also not reported. The aim of the present study is to report various primary immune deficiencies diagnosed in children at a tertiary care hospital, their clinical manifestations and laboratory profile.

MATERIALS AND METHODS

Case records of all children who were diagnosed to have a primary immunodeficiency disorder in the pediatric department at a tertiary care hospital in northern India over a period of 24 months (July 2004- Aug 2006) were reviewed. Children with HIV infection and those on

Correspondence and Reprint requests : Dr. S.K. Kabra, Additional Professor, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110029, India.

[Received April 25, 2007; Accepted January 4, 2008]

cancer chemotherapy/ chronic steroid ingestion were excluded from the study. All the patients had at least one or more of clinical criteria described for suspicion of immune deficiency.[4] Diagnosis of individual primary immune deficiency was based on typical clinical features along with laboratory abnormalities.[5]

Following Classification criteria of primary immunodeficiency was used.[5]

Humoral or antibody deficiency

Hypogammaglobulinemia: Cases with recurrent sinopulmonary infections with encapsulated bacteria and decreased age-matched immunoglobulin levels were sub-categorized in this group

Selective IgA deficiency: Study subjects with atopy, recurrent diarrhea respiratory infections and decreased age specific IgA levels were grouped in this category.

Combined or cellular deficiency

SCID (Severe Combined Immunodeficiency): Age of onset <1yr, atypical Mycobacterium infection, failure to thrive, diarrhea, disseminated CMV/ BCG infection and skin rash along with decreased age-matched T-cell numbers and immunoglobulins levels were classified into this group

Ataxia telangiectasia: Cases with ataxia, telangiectasia over bulbar conjunctiva and skin, cerebellar atrophy on CT head, repeated sinopulmonary infections, raised alpha fetoprotein levels and IgA deficiency were included in this group

Wiskott-Aldrich syndrome: Thrombocytopenia and abnormal platelet size, eczema and repeated infections

DiGeorge syndrome: Hypocalcemic seizures, hypoparathyroidism, cardiac disease, abnormal facies, infections and decrease T-cell number

Hyper IgM syndrome: Recurrent serious pyogenic infections and IgM levels beyond 1000mg/dl with decreased IgG and IgA levels

Phagocyte defects

Chronic Granulomatous disease (CGD): Deep-seated infections, abscess, granuloma formation and abnormal NBT dye reduction test as described by Baehner and Nathan.[6] Children showing <50% neutrophils reducing the dye were considered as homozygous for CGD, between 50-90% were considered carriers and > 90% were considered as normal.

Leukocyte adhesion defect (LAD): Serious bacterial infections, delayed umbilical cord separation at birth, poor wound healing, lack of pus associated with neutrophilia and abnormal neutrophil surface receptor CD18/CD11 levels suggest LAD

Hyper IgE syndrome: Chronic dermatitis, recurrent infections of lung with pneumatoceles, skin infections, bone fragility, failure to shed primary teeth and IgE levels beyond 1500 mg/dl

Clinical and laboratory details were recorded. Descriptive analysis was done to determine the age, gender and onset of symptoms, type of infections, organisms isolated, allergies, malignant conversion and follow up duration. As it was retrospective review of case record, clearance from ethics committee was not obtained.

RESULTS

Twenty-seven children (n=27, 21 boys, 6 girls) were diagnosed to have primary immunodeficiency in the 2-year period. The mean age of patients was 5.4 ± 4.6 yrs (2 months-16 years) with the age of onset of symptoms being 2.2 ± 2.6 years (range: birth to 9 years).

On subcategorizing cases based on symptom complex and available investigations: Fourteen children had phagocyte defects, 9 had combined or cellular defects and 4 had humoral or antibody defects (Table 1).

Common mode of presentation were recurrent/ persistent pneumonia in 19, recurrent/ persistent diarrhea in 10, deep seated abscesses in 8, allergy in 3, disseminated tuberculosis infection in 2, extensive fungal infections in 2 and 1 each of disseminated cytomegalo virus (CMV) infection, disseminated BCG disease, otitis media and meningitis respectively. Malignancy in form of Hodgkin's lymphoma and acute leukemia was seen in one child each in the study group (Table 1). Infectious agent was isolated in 16 cases at time of work up (Table 2).

Severe combined immunodeficiency (SCID) was diagnosed based upon history, examination and decreased CD3+, CD4+, CD8+ cells in 4 cases (table 1). The mean age at presentation was 3.3 ± 2.7 months with male to female ratio 1:1. The common clinical manifestations were recurrent/persistent pneumonia, hepatosplenomegaly, failure to thrive, and family history of sibling deaths.

DiGeorge syndrome was diagnosed in 4-month-old boy (case no 5, table I) with disseminated CMV infection (urine and saliva CMV PCR positive), decreased CD4 and CD8 counts, absent thymic shadow along with transpositions of great vessels (aorta and pulmonary artery) for which he was operated in neonatal life. Child had persistent fever, hepatosplenomegaly and pancytopenia. In spite of intravenous immunoglobulins (IVIG) and Gancyclovir the child succumbed to massive gastrointestinal bleeding secondary to CMV colitis indicated by mucosal biopsy done endoscopically.

Table 1. Clinical and Laboratory Profile of Primary Immunodeficiency Patients

S. No.	Age/ Sex	Clinical Features (onset)	Special Investigations (diagnosis)	Diagnosis	Age of onset of symptoms	Age at diagnosis	Outcome
Combined/ Cellular defects (n=9)							
1	5 mo/M	Disseminated T.B., rash, sibling deaths, recurrent diarrhea	CD4/CD8 undetectable, absent	Severe Combined (SCID)	1 mo	4 mo	Died
2	5 mo/F	Diarrhea, pneumonia, sepsis	CD4/CD8 289/09 cells/ mm^3	SCID	2 mo	5 mo	Died
3	2 mo/M	Disseminated T.B., family history of sibling deaths	CD4/CD8 03/05 cells/mm^3	SCID	15 d	2 mo	Died
4	3 mo/F	Disseminated BCG (Bacille Calmette Guerin)	CD4/ CD8 1687/157 cells/ mm^3	SCID (selective CD 8deficiency)	1.5 mo	2 mo	Follow-up
5	4 mo/M	Disseminated CMV, pancytopenia, GI bleed, Cong heart disease	CD4/ CD8 46/202 cells/ mm^3	DiGeorge syndrome	2 mo	4 mo	Died
6	12 yr/M	Recurrent sinopulmonary infections, ataxia, telangiectasia	AFP 202, IgA undetectable	Ataxia telangiectasia (AT)	1 yr	8 yr	Follow-up
7	10 yr/M	Recurrent Sinopulmonary infections, ataxia, telangiectasia, mediastinal mass	FFB 320, IgA undetectable Lymph node biopsy- Hodgkin's disease	AT with Hodgkin's lymphoma	1 yr	10 yr	Died
8	4 yr/M	Recurrent diarrhea, skin infections, eczema, thrombocytopenia	Abnormal platelet size	Wiskott-Aldrich syndrome	1 yr	3 yr	Died
9	1.5 yr/M	Fever, hepatosplenomegaly, anemia	IgM >1350, IgA 91, IgG 181mg/dl	Hyper IgM syndrome	12 mo	1.5 yr	Died
Humoral/ Antibody defects (n=4)							
10	16 yr/F	Recurrent pneumonia, diarrhea, Failure to thrive (FTT)	IgG 156, IgA 04, IgM 36 mg/dl	Hypogamma-globulinemia	2 yr	6 yr	Acute leukemia
11	10 yr/F	Recurrent pneumonia, Bronchiectasis	IgG 758, IgA 244, IgM 126 mg/dl	Hypogamma-globulinemia	4 yr	9 yr	Follow-up
12	9 yr/M	Bronchial Asthma, recurrent loose stools, allergic rhinitis	IgA <5 mg/dl	Selective IgA deficiency	4 yr	8 yr	Follow-up
13	2 yr/M	Repeated episodes of URI, cough, fever, nasal discharge	IgG 225, IgA <38, IgM <28 mg/dl	Hypogamma-globulinemia	10 mo	2 yr	Follow-up
Phagocyte defects (n=14)							
14	7 yr/M	Empyema, liver abscess, sepsis	NBT <5%cells, Mother: Normal	Chronic Granulomatous disease (CGD)	7 yr	7 yr	Died
15	3 mo/M	Rash, diarrhoea, pneumonia	NBT <5%cells, Mother: Carrier	CGD	3 mo	3.5 mo	Died
16	9 yr/M	Ilio-psoas and gluteal abscess, peritonitis	NBT <40%cells, Mother: Normal	CGD	9 yr	9 yr	Follow-up
17	5.5 yr/M	Recurrent abscess, diarrhoea, pneumonia	NBT <20%cells, Mother: Carrier	CGD	4 yr	5 yr	Follow-up
18	8.5 yr/M	Recurrent pneumonia, multiple pyogenic abscess	NBT <30%cells, Mother: Normal	CGD	1 yr	8.5 yr	Follow-up
19	1.5 yr/M	Recurrent pyoderma, diarrhoea, ear discharge	NBT <10%cells, Mother: Normal	CGD	6 mo	1.5 yr	Follow-up
20	9 yr/M	Multiple abscess (liver, muscles), recurrent diarrhea and ARI	NBT <10%cells, Mother: Normal	CGD	1 yr	9 yr	Follow-up
21	8 yr/M	Repeated LRTI, clubbing, fever, cough	NBT <30%cells, Mother: Normal	CGD	3 yr	8 yr	Died
22	14 yr/M	Repeated deep fungal infections (Brain, liver)	NBT <10%cells, Mother: Normal	CGD	9 yr	12 yr	Follow-up
23	4 yr/M	Recurrent diarrhea, pneumonia	NBT <5%cells, Mother: Normal	CGD	4 yr	4 yr	Follow-up
24	3 yr/M	Recurrent abscess (muscles, subcutaneous tissue, lung)	NBT <25%cells, Mother: Normal	CGD	3 yr	3 yr	Follow-up
25	8 yr/M	Recurrent pneumonia, liver abscess, dermatophyte infection	NBT <40%cells, Mother: Normal	CGD	2 yr	6 yr	Follow-up

Ataxia telangiectasia was seen in two brothers (cases no. 6, 7, Table 1). Both brothers had recurrent sinopulmonary infections, ataxia, cerebellar atrophy, and telangiectasia over bulbar conjunctiva, very low serum IgA and elevated alpha-fetoprotein levels. Elder brother developed biopsy proven Hodgkin's lymphoma and succumbed to his illness. Younger brother on follow up has repeated respiratory and gastrointestinal infections associated with absent IgA level and raised serum Alfa fetoprotein level.

Panhypogammaglobulinemia was present in 3 study subjects and selective IgA deficiency was seen in one. All patients had recurrent sinopulmonary infections. Child with IgA deficiency also had bronchial asthma and allergic rhinitis.

Thirteen boys (cases no 14-26, table 1) were diagnosed to have chronic granulomatous disease (CGD). The mean age was 5.9 ± 4.0 years. Ten children had recurrent pneumonia, 8 had recurrent abscess formations and 5 had recurrent/ persistent diarrhea. Nitro blue tetrazolium (NBT) test performed on study subjects showed <50% neutrophils reducing the dye in all cases (homozygotes). Mothers of 3 children were identified as carriers (heterozygote) by NBT test (50-90% positive cells). Three patients succumbed to their illness and 10 are on Co-trimoxazole and Itraconazole prophylaxsis on follow-up.

Leukocyte adhesion defect (LAD) was diagnosed in one patient. She manifested with delayed umbilical cord fall (after 30 days) followed by recurrent infection (pneumonia, diarrhea, oral thrush), ulcers (stomatitis), failure to thrive and pneumonia. She had neutrophilia (total leucocyte counts between 30-40000/ml) on investigations. On flow cytometry, CD11a and CD11b markers for leukocyte adhesion molecules were absent which confirmed the diagnosis.

DISCUSSION

Primary immunodeficiencies are inherited disorders of immune system function that predispose affected individuals to increased rate and severity of infection, immune dysregulation with autoimmune diseases and malignancy.[7] In the present series the number of cases diagnosed as suffering from primary immune deficiency in order of decreasing frequency were chronic granulomatous disease, severe combined immunodeficiency (SCID), Hypogammaglobulinemia, Ataxia telangiectasia, DiGeorge syndrome, Wiskott Aldrich syndrome, Hyper IgM syndrome and leucocyte adhesion defect. In view of a retrospective study from a tertiary care hospital, comparison with other studies may not be valid. In a retrospective analysis of 91 children with primary immune deficiency from Pediatric tertiary care hospital from USA it was observed that 67% had humoral

Table 1. *Continued*

S. No.	Age/ Sex	Clinical Features (onset)	Special Investigations (diagnosis)	Diagnosis	Age of onset of symptoms	Age at diagnosis	Outcome
26	10 mo/M	Lung abscess, brain abscess and FTT	NBT <40%cells, Mother: Carrier	CGD	5 mo	9 mo	Follow-up
27	2 yr/F	Delayed cord fall at birth, persistent pneumonia, neutrophilia	CD 11a and CD 11b absent	Leukocyte Adhesion Defect (LAD) type 1	Birth	2 yr	Follow-up

Table 2. Microorganisms Isolated in Primary Immunodeficiency Patients

Organism Isolated	Total Patients% (n=27)	Humoral deficiency% (n=4)	Combined deficiency% (n=9)	Phagocyte deficiency% (n=14)
Gram negative bacilli				
E. coli	2	-		1
Pseudomonas	1	-	1	1
Acinetobacter	1	-		1
Gram positive cocci				
Strep Pneum	1		1	
Staph aureus	1	-1		1
Coag. Neg. Staph	1			
Fungal infections				
Candida spp	2			2
Mucor spp	1			1
Trichorosporon	1			1
M. tuberculosis	2	-	2	-
M. bovis	1	-	1	-
Cytomegalovirus	1	-	1	1

or antibody deficiency, Cellular, combined and phagocytic disorders make up the remainder, each accounting for between 10% and 20% of the total. Complement deficiency is rare, comprising less than 1% of all primary immunodeficiency.[8] In another prospective study of 123 patients (median age 24.5 years; range 1-85 years) of primary immune deficiency the most common diagnosis was common variable immunodeficiency (32%), followed by IgG subclass deficiency and IgA deficiency.[4] The number of patients with immunoglobulin deficiency was less in our series possibly due to referral bias. Isolated IgA deficiency may produce milder symptoms and may not have reported/ referred to our center. Those with severe life threatening or long-standing or recurrent illness like combined immunodeficiency (SCID) and phagocytic disorders (CGD) were referred and admitted accounting for relatively more frequency of these conditions.

Infections are the most common presenting features of primary immunodeficiency. Infections may be repetitive, severe or refractory to therapy and caused by low virulence organisms. The commonest sites of infection include respiratory tract and gastrointestinal tract. The frequency of various infections in a report by Yarmohammadi *et al*[4] included: chronic sinusitis, chronic bronchitis, chronic otitis media, pneumonia and chronic diarrhea in order of decreasing frequency. Comparatively higher incidence of tuberculosis infection in our study is possibly because of high prevalence of tuberculosis in India.

The type of organism causing infection in primary immune deficiency disorders is also determined by the underlying disease. In a registry of 368 cases in United States residents with chronic granulomatous disease (CGD) pneumonia was the most prevalent infection (79% of patients; Aspergillus most prevalent cause), followed by suppurative adenitis (53% of patients; Staphylococcus most prevalent cause), subcutaneous abscess (42% of patients; Staphylococcus most prevalent cause), liver abscess (27% of patients; Staphylococcus most prevalent cause), osteomyelitis (25% of patients; Serratia most prevalent cause), and sepsis (18% of patients; Salmonella most prevalent cause).[9] In present series 13 children with CGD had recurrent infections of multiple sites and included recurrent deep seated abscess (liver abscess, pyomyositis, subcutaneous abscess) in 9, six patients presented with recurrent pneumonia, 3 had diarrhea and one presented with sepsis. The organisms isolated were gram negative bacilli, staphylococcus, candida spp, mucor sp and CMV. The clinical syndromes were similar but difference in organisms may be due to less numbers, different environmental conditions and less aggressive investigations for identification of organisms.

Among other non-infectious clinical symptoms which had given a clue to the diagnosis of primary immune deficiency were: 1) neurological manifestations like ataxia and cerebellar atrophy, which was present in two of our patients and the diagnosis was suspected by presence of bulbar telangiectasia and recurrent sinopulmonary infections. (2) Cardiac defect (conotruncal abnormalities) and absent thymus along with disseminated CMV infection prompted us to diagnose DiGeorge syndrome. (3) Eczema, diarrhea and persistent thrombocytopenia associated with repeated infections in a boy made us diagnose Wiskott Aldrich syndrome. Delayed cord fall and persistent neutrophilia with lack of pus suggested diagnosis of leukocyte adhesion defect.

Autoimmune diseases and malignancies are complications of many immunodeficiencies.[10] Immunological defect or dysregulation can lead on to autoimmune diseases like vasculitis, arthritis. None of the study patients had autoimmune disease. However, two of our study patients developed acute leukemia and Hodgkin's disease respectively.

Live vaccines (BCG and oral OPV) had been administered in all SCID patients before presentation and 75% developed disseminated tuberculosis, in one of the case we could prove M. bovis strain suggesting disseminated BCG infection. Child with DiGeorge syndrome had received blood during cardiac surgery and probably acquired CMV infection. These case scenarios highlight the need to bring awareness among general pediatricians for avoiding live vaccines in suspected case of primary immunodeficiency and a policy change of using only irradiated, CMV negative, lymphocyte depleted cellular blood products among all immunodeficient patients.[11,12]

The limitation of study includes: retrospective nature, study from a referral center and non-availability of some advanced molecular diagnostic tests. Due to retrospective nature we had access to the main results as the other details were not recorded in all the cases. It is not possible to estimate the incidence of primary immune deficiency for hospitalized children because of referral bias. For diagnosis of CGD we used conventional test in form of NBT test. We could not use flow cytometry test using Dihydro Rhodamine 123 fluorescence (DHR test) test that is more accurate.[13] To overcome this limitation we tried to repeat the test if it was borderline.

In conclusion, primary immunodeficiency disorders do occur in our country, though the exact prevalence is not known. There is need for high index of suspicion for immune deficiency. Children presenting with repeated infection due to usual or unusual organisms (opportunistic infections), atypical courses of infections, poor response to conventional treatment and increased complications following infection should be evaluated for primary immune deficiency. Awareness about these disorders may improve the diagnosis of these conditions and help in appropriate management. There is a need to

share experience and data on these rare conditions at a national and international level and build support groups so that both patients and families afflicted with these ominous disorders are guided well.[14]

REFERENCES

1. Salaria M, Poddar B, Parmar V. Hyperimmuneglobulin E syndrome. *Indian J Pediatr* 2001; 68: 87-90.
2. Shah I. Severe Combined Immunodeficiency. *Indian Pediatr* 2005; 49 : 819-822.
3. Shah I. Hyper IgM syndrome with tuberculous osteomyelitis and scrofuloderma. *Indian Pediatr* 2005; 42 : 952-953.
4. Yarmohammadi H, Estrella L, Doucette J, Cunningham-Rundles C. Recognizing Primary Immune Deficiency in Clinical Practice. *Clin Vaccine Immunol* 2006; 13: 329-332.
5. Stiehm ER, Ochs HD, Winkelstein JA. Immunodeficiency disorders: general considerations. In Stiehm ER, Ochs HD and Winkelstein JA, eds. *Immunologic Disorders in Infants & Children*, 5th ed. London; England, Elsevier Saunders, 2004: 289-355.
6. Baehner RL, Nathan DG. Leukocyte oxidase: defective activity in chronic granulomatous disease. *Science* 1967; 155 : 835-836.
7. Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM *et al.* Practice Parameters for the diagnosis and management of primary immunodeficiency. *Ann Allergy, Asthma Immunol* 2005; 94 : S1-S63.
8. Javier FC 3rd, Moore CM, Sorensen RU. Distribution of primary immunodeficiency diseases diagnosed in a pediatric tertiary hospital. *Ann Allergy Asthma Immunol* 2000; 84: 25-30.
9. Winkelstein JA, Marino MC, Johnston RB Jr, Boyle J, Curnutte J, Gallin JI, *et al.* Chronic granulomatous disease: report on a national registry of 368 patients. *Medicine (Baltimore)* 2000; 79: 155-169.
10. Taylor AM, Metcalfe JA, Thick J, Mak YF. Leukemia and lymphoma in ataxia telangiectasia. *Blood* 1996; 87 : 423-438.
11. Recommendations of the Advisory Committee on Immunization Practices (ACIP): use of vaccines and immune globulins for persons with altered immunocompetence. *MMWR* 1993; 42 : 1-18.
12. Moor AC, Dubbelman TM, Van Steveninck J, Brand A. Transfusion-transmitted diseases: risks, prevention and perspectives. *Eur J Haematol* 1999; 62 : 1-18.
13. Atkinson TP, Bonitatibus GM, Berkow RL. Chronic granulomatous disease in two children with recurrent infections: family studies using dihydrorhodamine based flow cytometry. *J Pediatr* 1997; 130 : 488-491.
14. Shearer WT, Fischer A. The last 80 yrs in primary immunodeficiency: How far we come, how far need we go? *J Allergy Clin Immunol* 2006; 117: 748-752.