

Review Article

Primary Immunodeficiency Disorders – An Update

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Introduction:

Primary immunodeficiency disorders (PIDs) are rare inherited conditions that predispose individuals to infections that are recurrent due to unusual organisms. PIDs are also often associated with autoimmune, haematological and malignant disorders¹. Primary immunodeficiency have many clinical similarities with, but distinct from, secondary immunodeficiency that may occur during certain viral infections, during treatment of systemic autoimmune disease, in association with cancer chemotherapy, after immunosuppression to prevent graft rejection after transplantation². Primary immunodeficiencies (PIDs) comprise more than 130 different disorders that affect the development, function, or both of the immune system³. In most cases PIDs are monogenic disorders that follow a simple mendelian inheritance; some PIDs recognizes a more complex polygenic origin. Disease penetrance and expression variability and interactions between genetic and environmental factors can also contribute to the phenotypic diversity of PIDs. With the exception of IgA deficiency (IgAD), all other forms of PIDs are rare and have an overall prevalence of approximately 1:10,000 live births; however, a much higher rate is observed among populations with high consanguinity rates or among genetically isolated populations⁴. Primary immunodeficiencies can be divided into subgroups based on the component of the immune system that is affected. This article reviews the characteristics of some of the more common primary immunodeficiencies and provides an approach to the initial evaluation of patients suspected of having these disorders.

Immune system of body:

The body's immune response is made up of a diverse network of defenses, including physical barriers, cellular components, and soluble mediators. The normal immune system has two "arms": first, it mounts rapid, nonspecific responses (innate immune responses) to

initial infection; later, it mounts adaptive immune responses specific to a particular pathogen. Together, these arms work to maintain normal host function and resistance to infection. Disruption of any part of the immune response can result inability to control infection and subsequent illness⁵. The innate immunity responds to infection regardless of previous exposure to the agent and includes polymorpho-nuclear leucocytes, dendritic & mononuclear phagocytic cells, various receptors that recognize common pathogen organisms and the compliment system. Acquired immunity is a highly specific response that include T lymphocytes, B lymphocytes and natural killer cells. Again acquired immunity can be divided into cellular and humoral responses. The cellular immune response is mediated primarily by T cells and limits intracellular infections by organisms such as viruses, parasites, and mycobacteria. Antibodies, the key feature of the humoral response, are produced by activated B cells to help control the spread of extracellular pathogens. T-lymphocyte and B-lymphocyte responses are not independent of one another. Thus, defects in either cell type have the potential to affect both cellular and humoral immunity to varying degrees⁶.

Characteristics of Primary Immunodeficiencies:

PIDs are most often categorized according to immune mechanisms that are disturbed. These categories include the defect of specific immunity that are subdivided into humoral or antibody deficiencies, cellular deficiencies and combined deficiencies that affect both humoral and cellular deficiencies. There are also defects in the innate immunity and the phagocytic and compliment system defects. Of all of these categories, antibody deficiencies together account for approximately half of all PIDs⁶.

When to suspect Antibody Deficiency Disorders

Defective antibody production causes increased susceptibility, mostly to bacterial infections (Table-I) that typically involve the upper and lower respiratory tract (otitis, sinusitis, and pneumonia) but might also cause abscesses in the skin or other organs, meningitis, urinary tract infections, and arthritis. Recurrent viral infections are also common. Intestinal Giardia species infection can cause protracted diarrhea. Antibody deficiencies might depend on a

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variety of defects that interfere with B-cell development, maturation, and/or function.⁷ Antibody deficiency disorders include selective Ig A deficiency, common variable immunodeficiency disorders (CVID), congenital agammaglobulinemias (both X-linked and autosomal recessive inheritance) and transient hypogammaglobulinemias of infancy (THI)³.

Bruton's or X-linked agammaglobulinemia the most common form of early onset agammaglobulinemias, is caused by mutation or absence of the Bruton's tyrosine kinase gene. Early B-cell development is arrested, and serum immunoglobulins (IgG, IgA, IgM) are markedly deficient or totally absent. Onset of recurrent bacterial infections is usually at the end of the first year of life⁸.

Common variable immunodeficiency disorders (CVID) are another important form of antibody deficiency disorders defined by severe reduction in at least two Ig isotypes with impaired antibody production in response to immunization antigens or natural infections. In addition to recurrent infections of the respiratory tract (sinusitis, otitis, bronchitis, and pneumonia) caused by common bacteria (eg, nontypeable *Haemophilus influenzae* and *Streptococcus pneumoniae*), some patients with a CVID are highly prone to autoimmune manifestations (cytopenias and inflammatory bowel disease), granulomatous lesions, lymphoid hyperplasia, and tumors (especially lymphomas)⁹.

Transient hypogammaglobulinemia of infancy (THI) have low immunoglobulin levels that spontaneously return to normal, usually within 2 years of age. Although many subjects with THI remain asymptomatic, this condition is associated with a higher rate of recurrent infections, especially upper respiratory tract infections of viral origin¹⁰.

When to suspect T-cell or Combined T and B-cell immunodeficiency disorders

Combined immunodeficiency disorders (CID) comprise a heterogeneous group of disorders with impaired development, function or both of T lymphocytes associated with a defective antibody response. The latter might result from intrinsic defects in B lymphocytes or might reflect inadequate T helper cell activity¹¹. These primary immunodeficiency disorders are generally more severe than antibody deficiencies. Affected patients often present early in life with failure to thrive and disseminated infection. DiGeorge syndrome is one of the most recognized disorders in this category, and severe combined immunodeficiency (SCID) is the most severe. General features of this class of diseases include overwhelming viral and fungal

infections¹². Patients with SCID present early in life with infections of bacterial, viral, or fungal origin (Table-I). Many infants with SCID have chronic diarrhea, leading to failure to thrive. Skin rash might reflect graft-versus-host disease caused by maternal T-cell engraftment in infants with SCID or tissue damage caused by infiltration by activated autologous T lymphocytes, as typically seen in Omenn syndrome¹³. Laboratory findings typically demonstrate severe lymphopenia. About one half of SCID cases are X-linked, and one half are autosomal recessive¹⁴.

Other severe cellular or combined defect present with varied clinical symptoms as listed briefly in Table-II .

When to suspect Phagocytic cell defects:

Phagocytes comprised mainly of neutrophils, monocytes and macrophages are playing a key role in the defense against bacteria and fungi; accordingly, patients with defects of phagocytic cell number, function, or both experience recurrent and severe infections of fungal (especially *Candida* and *Aspergillus* species) and bacterial origin. Respiratory tract and cutaneous infections predominate, but deep-seeded abscesses are also common. Recurrent oral stomatitis is present in most cases¹⁴. Phagocytic disorders are not associated with increased susceptibility to viral or protozoal infections, or increased risk for malignancy. Disorders include chronic granulomatous disease, leukocyte adhesion deficiency, and Chédiak-Higashi syndrome, Cyclic neutropenia, Severe congenital neutropenia, Hyper-Ig E syndrome¹⁵.

Chronic granulomatous disease (CGD), the most frequently diagnosed phagocytic primary immunodeficiency, is more common in males than in females. In this disease, deficiency of nicotinamide adenine dinucleotide phosphate oxidase in phagocytes results in defective elimination of extracellular pathogens such as bacteria and fungi. Patients with chronic granulomatous disease are more susceptible to recurrent severe infections (skin, liver and perirectal abscesses, pneumonia and lymphadenitis) with catalase-positive organisms e.g., staphylococci that require phagocytic activity for clearance. *Aspergillus* infection is the most common cause of death in patients with phagocytic primary immunodeficiency disorders.¹⁶ Patients with neutropenia and those with leukocyte adhesion deficiency (LAD) tend to have recurrent cellulitis, periodontal disease, otitis media, pneumonia and rectal or gastrointestinal infections with diminished inflammation and lack of pus formation¹⁷.

Table-I
Type of infections associated with major categories of PIDs⁷

| Organism | Antibody deficiencies | CIDs | Phagocytic defects | Complement deficiencies |
|--------------|--|--|--|---|
| Viruses | Enteroviruses | All, especially:CMV, respiratory syncytial virus, EBV, parainfluenza type 3 | No | No |
| Bacteria | <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i> , <i>Pseudomonas aeruginosa</i> , <i>staphylococcus aureus</i> , <i>Neisseria meningitidis</i> , <i>Mycoplasma pneumoniae</i> | As for antibody deficiencies, also: <i>Salmonella typhi</i> , <i>Listeria monocytogenes</i> , enteric flora | <i>S aureus</i> , <i>P aeruginosa</i> , <i>Nocardia asteroides</i> , <i>S typhi</i> | As for antibody deficiencies:especially <i>N meningitidis</i> in deficiency of late components |
| Mycobacteria | No | Nontuberculous, including BCG | Nontuberculous, including BCG | No |
| Fungi | No | <i>Candida</i> species, <i>Aspergillus</i> species, <i>Cryptococcus neoformans</i> , <i>Histoplasmosis capsulatum</i> | <i>Candida</i> species, <i>Aspergillus</i> species | No |
| Protozoa | <i>Giardia lamblia</i> | <i>Pneumocystis jiroveci</i> , <i>Toxoplasma gondii</i> , <i>Cryptosporidium parvum</i> | No | No |

Table-II
Most common T-cell and combined immunodeficiencies and distinctive features.¹³

SCID: failure to thrive, chronic diarrhea, oral thrush, recurrent or severe bacterial, viral and/or fungal infections

Wiskott-Aldrich syndrome: easy bruising, eczema, recurrent otitis media, diarrhea, thrombocytopenia with small platelets

DiGeorge syndrome: hypoparathyroidism, cardiac malformations, dysmorphic features, variable T- and B-cell defects

Anhydrotic/hypohidrotic ectodermal dysplasia with immunodeficiency: recurrent mycobacterial or pyogenic infections, with or without skin, hair, and nail abnormalities; poor fever responses

XLP: hypogammaglobulinemia, persistent or fatal EBV infection

Chronic mucocutaneous candidiasis: recurrent oroesophageal and skin *Candida* species infection

Table-III
*Ten warning Signs of Primary Immunodeficiency Disorders*²¹

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|--|
| Eight or more ear infections in one year |
| Two or more serious sinus infections in one year |
| Two or more bouts of pneumonia in one year |
| Two or more deep-seated infections, or infections in unusual areas |
| Recurrent deep skin or organ abscesses |
| Need for intravenous antibiotic therapy to clear infection |
| Infections with unusual or opportunistic organism |
| Failure to gain weight |
| Persistent Oral thrush |
| Family history of primary immunodeficiency |

Table-IV
*Laboratory Testing for Primary Immunodeficiency Disorders*²⁴

| Laboratory test | Screens for... | What to look for... |
|--|---|--|
| Complete blood cell count with manual Differential | T-cell, B-cell, and mixed B-cell and T-cell defects | Decreased numbers of T cells, B cells, or platelets |
| Delayed-type hypersensitivity skin test | T-cell defects | Negative result signaling impaired T-cell response |
| Serum IgG, IgM, and IgA levels | Humoral immunodeficiencies | Decrease in any or all of the serum immunoglobulins |
| Antibody testing to specific antigens Vaccination | Humoral immunodeficiencies | Decreased or absent antibody after response to vaccination |
| Total hemolytic complement assay (CH50) | Complement deficiencies | Decreased or absent proteins if there is a deficiency in the classic pathway |
| Nitroblue tetrazolium test | Phagocytic disorders | Abnormal test result |

When to suspect Complement Disorders

Complement disorders represent the rarest form of primary immunodeficiencies, accounting for only 2% of this diseases¹⁸. The clinical setting in which complement defects should be suspected depend on the site of defect. Abnormalities in the early components of the classical complement pathway (C1, C4 and C2) typically manifest as systemic lupus erythematosus- like autoimmunity but recurrent sino-pulmonary infections are also seen in C2 deficiency¹⁹. Defects in the late components of complement (C5-C9) present with increased susceptibility of infections with Neisseria species. Factor H deficiency is associated with atypical (not associated with diarrhea) hemolytic uremic syndrome or glomerulonephritis.

Finally, C1 esterase inhibitor deficiency causes hereditary angioedema, whereas DAF (decay-accelerating factor) and CD59 defects are seen in patients with paroxysmal nocturnal hemoglobinuria²⁰.

Diagnosis of Primary immunodeficiencies:

The National Institute of Child Health and Human Development recently initiated an educational program to raise awareness of primary immunodeficiencies. As a part of this program, the Jeffrey Modell Foundation developed a list of warning signs for primary immunodeficiency²¹. Details medical history (age at onset, and severity and site of infections) might provide important insights into the possible underlying mechanisms of immunodeficiency. Additional aspects of past medical history might also help. A history of

HIV infection is very important in the differential diagnosis of SCID. Family history is also important in the approach to PID. Physical examination can also provide important hints. Patients with agammaglobulinemia show absence of tonsils and other lymphoid tissues. Ataxia and ocular telangiectasias are observed in ataxia-telangiectasia, microcephaly is common in PIDs associated with defects in DNA repair, petechiae and other bleeding manifestations associated with eczema are highly suggestive of WAS, and patients with immuno-osseous disorders have short stature³.

Laboratory Evaluation

When primary immunodeficiency is suspected, initial laboratory studies include a complete blood cell count (CBC) with manual differential, quantitative immunoglobulin measurement (IgG, IgM, IgA), measurements of functional antibodies against immunized antigens (protein and carbohydrate) and blood group antigens (isohemagglutinins) and also delayed-type hypersensitivity skin tests (Table 4). In most instances, a normal CBC eliminates the diagnosis of T-cell defects or combined B-cell and T-cell defects²². If the ESR is normal, chronic bacterial or fungal infection is unlikely. If an infant's neutrophil count is persistently elevated in the absence of any signs of infection, a leukocyte adhesion deficiency should be suspected. If the absolute neutrophil count is normal, congenital and acquired neutropenia and leukocyte adhesion defects are excluded. If the absolute lymphocyte count is normal, the patient is not likely to have a severe T-cell defect. Lymphopenia and marked reduction of T-Lymphocyte count is a hallmark of SCID but HIV infection must be excluded. If the platelet count is normal or platelet size is normal, Wiskott-Aldrich syndrome is excluded²³. If a CBC and a manual differential were performed on the cord blood of all infants, severe combined immunodeficiency (SCID) could be detected at birth, and lifesaving immunologic reconstitution could then be given to all such infants⁷.

Additional testing focuses on determining the presence or absence of B & T cells by using flow cytometry. In antibody deficiency disorder it is particularly useful as a marker for congenital forms of agammaglobulinemia because this group of disorders are typically characterized by absent or extremely decreased circulating B cell numbers based on underlying defects that block B cell development. HIV

infection has to be ruled out in all patients of cellular immunodeficiencies and this requires testing for the presence of virus rather than serologic testing for anti-HIV antibody²⁴.

Management of patients with Primary immunodeficiency:

a) Intravenous Immunoglobulin (IVIG): IVIG is now considered as the standard therapy for most of the antibody deficiencies. Children with XLA and CVID need 3-4 wky injections of IVIG. This treatment is very expensive but it can result in an almost normal life span. IVIG is used as replacement therapy in various forms of hypogammaglobulinemia. Administration of IVIG can be associated with several side effects. The infusion must be started very slowly and the child be monitored for allergic reactions, which may include anaphylaxis. Subcutaneous immunoglobulin (SCIG) preparations are now available in western world²⁵.

b) Bone marrow transplants: From HLA-identical donors can be curative in patients with cellular immune deficiencies such as severe combined immunodeficiency, Wiskott-Aldrich syndrome and Hyper IgM syndrome. For it's success, the procedure has to be done in early infancy²⁶.

c) Antimicrobial prophylaxis: Some children with IgG subclass deficiency may require daily prophylactic therapy (usually cotrimoxazole). Long term cotrimoxazole and itraconazole prophylaxis and Interferon γ injections has greatly improved the management of chronic granulomatous disease. In compliment deficiency disorders daily prophylaxis is essential for prevention of infection. For C1 esterase inhibitor deficiency, prophylactic danazol/stanozolol therapy have been used with very good results²⁵.

d) Immunization:

Individual of compliment deficiencies required immunizations for encapsulated bacteria (e.g, pneumococcal vaccine, Haemophilus b conjugate vaccine, meningococcal polysaccharide vaccine).²⁷ Use of live attenuated vaccines must be avoided to prevent uncontrolled vaccine associated infections.

e) Gene therapy

Gene therapy has shown to be effective for patients with Adenine deaminase (ADA) deficiency and with X linked SCID leading to survival with immune reconstitution. It is anticipated that gene therapy will be considered for a growing number of PIDs in the years to come²⁸.

Conclusion:

PIDs are still considered as uncommon diseases by most of the physicians and paediatricians. This is unfortunate that many of the physicians and paediatricians are not sufficiently aware about this problem. So our PID cases are often offered inappropriate diagnosis and inadequate treatment by the caregivers. It is very much essential to increase awareness about PID not only among physicians community but also among general population. Long time survival is possible with early diagnosis and adequate treatment with life long anti bacterial and anti fungal prophylaxis.

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