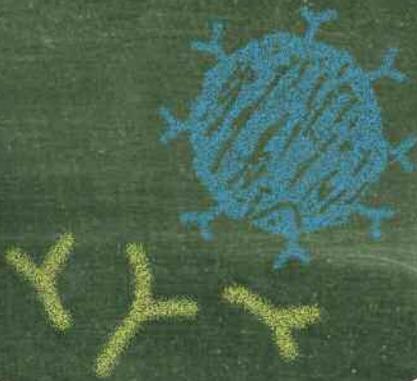


# A Primer on Primary Immunodeficiency Disorders



Although there are more than 200 identified PIs, the more common and classically described represent the hallmarks of these disorders.

By Bob Geng, MD



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**THE FIRST PRIMARY** immunodeficiency disease (PI) was described in 1952 by Colonel Ogden Bruton. He wrote about a young boy suffering recurrent respiratory infections due to inability to make specific antibodies, who was successfully treated with immune globulin (IG) replacement therapy. This famous case — later coined “Bruton’s agammaglobulinemia” caused by a genetic defect in B-cell maturation found on the X chromosome — led to the birth of the field of PIs.

Fortunately, PIs are not common disorders. However, they are not as rare as some have previously believed. There are currently more than 200 characterized distinct PIs, and that number is growing due to advances in immunology and genetics. The prevalence of diagnosed PI in the U.S. is approximately one in 2,000 patients, and the incidence of newly diagnosed PI is approximately one in 10,000 patients. This is likely an underestimate, though, since it takes into account only the diagnosed cases, and there are many cases that persist for long periods without a proper diagnosis.

## Review of the Immune System

Before delving into an in-depth discussion of the various types of PIs, it is important to review the basic workings of the human immune system. The immune system is divided into the innate and the adaptive systems. The innate system is nonspecific, but it is the first line of host defense. The cells associated with the innate system include neutrophils, macrophages and dendritic cells. The humoral components of the innate system include complement proteins and other molecules that defend against microbes in a nonspecific fashion.

The adaptive immune system, on the other hand, is specific and has immunologic memory. The cells involved in the adaptive system are B and T cells. T cells are further divided into T-helper cells and cytotoxic T cells. The humoral components include the immunoglobulins: IgM, IgG, IgA and IgE.

Of all the PI conditions, around 65 percent are antibody deficiencies that are a result of some form of defect in immunoglobulin production. Around 5 percent are pure T cell deficiencies, 15 percent are combined cellular and antibody deficiencies, 10 percent are disorders of the innate immune cells and 5 percent are complement deficiencies and other disorders of the innate immune system.

## Antibody Deficiencies

One of the most frequently diagnosed antibody deficiencies is common variable immune deficiency (CVID). Rather than one single disorder, CVID actually represents a whole spectrum of

conditions. It can often present later in life, frequently in the third to fourth decades of life. Only a few identified single gene defects have been found, but the majority of cases are associated with unknown mechanisms. The B cell count may be depressed or normal, but it is always associated with low IgG plus either low IgA or IgM. There are poor specific antibody titers and poor responses to vaccines. The conservative estimate on prevalence is around one in 25,000.

The clinical presentation of CVID is characterized by recurrent respiratory infections and gastrointestinal infections. It is also associated with complications of autoimmune disease, chronic lung disease, inflammatory gastrointestinal disease and malignancies. Treatment includes IG replacement therapy and, in some cases, prophylactic antibiotics. The incidence of autoimmune complications rises when there is a lack of class switched memory B cells. Unfortunately, the average time from symptom onset to diagnosis is still over a decade due to poor recognition and lack of early diagnostic testing.

## THE MOST COMMON FORM OF ANTIBODY DEFICIENCY IS SELECTIVE IGA DEFICIENCY WITH AN INCIDENCE OF ONE OUT OF 400.

As mentioned, agammaglobulinemia was the first discovered PI. Bruton’s agammaglobulinemia represents 90 percent of all cases and only presents in boys, since it is an X-linked disorder. An autosomal recessive form also exists and represents about 10 percent of cases. This condition is also associated with absence of B cells along with absence of immunoglobulin. The classic presentation includes respiratory tract infections, diarrhea, meningitis, cellulitis and sepsis. Treatment includes IG replacement therapy, and some experts advocate for the use of prophylactic antibiotics.

The most common form of antibody deficiency is selective IgA deficiency with an incidence of one out of 400. Most patients are asymptomatic, but some individuals may develop frequent and longer respiratory infections, allergic disease and autoimmune disease (such as celiac disease). Selective IgA defi-

ciency patients need careful monitoring by an immunologist since some of these cases may evolve into CVID.

When the number of B cells and the quantity of immunoglobulins are normal, their function can still be abnormal. This is the case for specific antibody deficiency (SAD), which is diagnosed by testing against titers to the 23 serotypes of *Streptococcus pneumoniae*, or pneumococcus. SAD patients demonstrate an inadequate level of post-vaccination titers to 50 percent of the pneumococcal serotypes. Clinical features of SAD include frequent respiratory infections and allergic disease. Treatment includes antibiotic prophylaxis and IG replacement therapy.

The first class of immunoglobulins produced is IgM. When the body is incapable of switching to other classes of immunoglobulins, hyper-IgM syndrome occurs either because T helper cells are unable to communicate effectively to B cells or the actual machinery of class switching is dysfunctional. Clinical presentation is similar to severe forms of CVID. IgM levels do not need to be significantly elevated, and sometimes they can be normal appearing. However, the other classes of immunoglobulins are extremely low. Treatment includes IG replacement therapy, as well as bone marrow transplant.

## A NUMBER OF DISTINCT CELLULAR DISORDERS OF THE INNATE SYSTEM ARE GENERALLY CAUSED BY DEFECTS OF NEUTROPHIL FUNCTION.

### **Severe Combined Immunodeficiency (SCID)**

SCID is the classic “bubble boy” syndrome, and it is a medical emergency. This syndrome affects both the cellular and antibody aspects of immunity. It occurs in one of every 50,000 live births. Classic clinical presentations are failure to thrive, multiple infections, diarrhea and low lymphocyte counts. Without treatment, it is usually fatal before 2 years of age. Often, babies may initially appear normal at birth, but develop infections very quickly. T cells are always affected, but depending on the syndrome, B cells and/or natural killer (NK) cells can also be affected.

Time-sensitive diagnosis relies on newborn screening, which is currently used in many states, but it is still not universal.

Confirmatory tests include flow cytometry that looks at exact numbers of T, B and NK cells, and genetic tests that look at the presence of specific defects. Treatment includes bone marrow/stem cell transplant, IG replacement therapy, enzyme replacement and gene therapy, which is currently still experimental. If diagnosed early and the patient receives a transplant before 3.5 months old, survival can be as high as 94 percent. However, if the diagnosis is made late, and transplant occurs after that time, survival decreases to less than 70 percent.

### **DiGeorge Syndrome**

One of the classic defects mainly affecting T cells is DiGeorge syndrome, which was discovered in 1965 by Dr. Angelo DiGeorge. These patients have a deletion of chromosome 22q11, which affects thymic development. Characteristics include typical facial features of hypertelorism, anti-mongoloid slant of eyes and low-set ears. Only 0.5 percent of all cases are “complete DiGeorge” syndrome. Other clinical presentations can include cardiac malformations, speech delay, cellular immunodeficiency, low serum calcium and autoimmunity. A very small number of partial DiGeorge patients do eventually need IG replacement therapy due to poor production of B cells caused by insufficient T-cell stimulation.

### **Cellular Defects of the Innate Immune System**

A number of distinct cellular disorders of the innate system are generally caused by defects of neutrophil function. Neutrophils are the body’s first cellular line of defense against invading microbes. They can either be defective due to an inability to produce necessary compounds to destroy ingested microbes, as in the case of chronic granulomatous disease (CGD); an inability to release synthesized compounds that can destroy ingested microbes, as in Chediak-Higashi syndrome; or an inability to migrate out of the blood vessels into the areas of microbe invasion, as is the case in leukocyte adhesion deficiencies (LADs).

CGD is a condition in which there is impaired ability for neutrophils to generate reactive oxygen species and bleach to destroy ingested microorganisms. It occurs in one out of 200,000 people. The inheritance pattern can be both X-linked (65 percent) and autosomal recessive (35 percent). Clinical presentation can include pneumonia, skin abscesses and development of granulomas. Common invading organisms include *Staph aureus*, *Burkholderia*, *Serratia*, *Nocardia* and *Aspergillus*. Acute treatment includes antibiotics and antifungals targeted toward the invading organisms. Chronic management includes prophylactic therapy often involving Bactrim, antifungals with

Aspergillus coverage and interferon gamma for immunomodulation. Currently, the only approved definitive therapy is bone marrow/stem cell transplant.

Chediak-Higashi syndrome is a disorder that results in neutrophils with giant granules and an inability to mobilize the enzymes in the granules. The defect is in the LYST gene that results in impaired lysosomal trafficking. The clinical presentation includes albinism in the eyes and skin, frequent bacterial infections, neurologic defects and metallic silver-gray sheen in the hair. Treatment is bone marrow/stem cell transplantation, which improves the immunologic defects but does not lead to cure of the neurologic defects.

LAD is characterized into types I, II and III. Types I and III are similar, both caused by an inability of white cells in the blood vessels to migrate out of the vessels into the affected tissue. As a result, the white blood cells are trapped in the blood vessels, keeping them from getting to the areas of infection/inflammation, where they are needed to combat invading microbes. LAD type II is caused by an inability to control the rolling of white blood cells in the blood vessels so they are unable to slow down in order to migrate out of the vessels. All LAD types can cause a delayed separation of the umbilical cord, dental disease, high white blood cell count, bacterial infections of the skin and infections in the gastrointestinal and respiratory tracts. Clinical presentation can vary in severity.

## Complement Disorders

The complement system can be activated through three different pathways: classical, alternative and mannose-binding lectin. Defects can occur in each of those pathways. In addition to these pathways, the complement system is divided into early components and late components of activation. Defects in early components generally result in a clinical presentation of both immunodeficiency and autoimmunity. Defects in late components result in susceptibility to disseminated meningococcal infections. Lastly, aside from the main components of complement activation, there can also be defects that occur in associated components, which can lead to a variety of clinical diseases, ranging from hemolytic uremic syndrome and kidney dysfunction to hereditary angioedema.

## Hyper IgE Syndromes

There are two main types of hyper IgE syndrome: autosomal dominant Job's syndrome and autosomal recessive hyper IgE.

Job's syndrome patients can present with distinctive facial features of wide nasal width, facial asymmetry and hypertelorism.

From an immunodeficiency perspective, they can present with recurrent boils due to Staph aureus infections, eczema, Candida yeast infections, high blood eosinophil counts and lung abscesses. The mechanism of disease is a defect in the cell-signaling molecule STAT3.

Autosomal recessive hyper IgE syndrome does not present with any typical facial features. These patients suffer from recurrent respiratory infections, as well as skin infections with herpes virus, human papilloma virus and molluscum infections. They can also present with a significant amount of allergic disease. The known mechanism of disease is a defect in the molecule DOCK8.

## Susceptibility to Atypical Mycobacterial Infections

Patients who are susceptible to atypical mycobacterial infections are prone to nontuberculosis Mycobacterium, including Mycobacterium avium, fortuitum, bovis and Bacillus Calmette-Guérin. In addition, they demonstrate susceptibility to salmonella, which is an intracellular bacteria, but is not a mycobacteria. The normal clearance of intracellular bacteria requires normal function of Interleukin-12 (IL-12) and interferon gamma. Normal function means the innate immune system starts producing IL-12 to stimulate T cells that in turn produce interferon gamma to stimulate the innate cells (macrophages) to kill bacteria. There are many steps in this process, so defects along any of the steps in the IL-12 and interferon-gamma pathway can lead to an abnormal clearance of intracellular bacteria. Patients who have a defect in the interferon-gamma receptor have a worse prognosis, and patients with defects in the IL-12 receptor have a better prognosis in general because they can be treated with interferon-gamma supplementation (Actimmune).

## More PIs, Growing Insight

There are more than 200 distinct types of PIs that have been described, and more PIs are being discovered given our advances in understanding basic immunology and genetics. This article touched only on some of the common and classically described syndromes. As such, it is not meant to be an exhaustive list of all PIs. Through patients with these disorders, the scientific community is gaining invaluable insights into the workings of the human immune system and how small defects can lead to immense changes and profound disease. ■

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