



CHAPTER

14

Other Important Primary Immunodeficiency Diseases

In addition to the major primary immunodeficiencies described in other chapters, there are other less common, but well-described, immunodeficiencies. These less common disorders can be classified into four categories:

Less common antibody deficiencies

Less common cellular deficiencies

Less common phagocytic cell deficiencies

Less common innate immune defects

Less Common Antibody Deficiencies

Similar to the patients described in the chapters on X-linked Agammaglobulinemia (XLA), Hyper IgM Syndrome, Selective IgA Deficiency, Common Variable Immunodeficiency, IgG Subclass Deficiency and Specific Antibody Deficiency, individuals with less common antibody deficiencies usually present with upper respiratory infections or infections of the sinuses or lungs. Laboratory studies show low immunoglobulins and/or deficient antibody function. The patients often improve with antibiotics but get sick again when these are discontinued. These illnesses include the following disorders:

Autosomal Recessive Agammaglobulinemia

These patients resemble patients with XLA including a profound deficiency of immune globulins, antibodies and B-cells, but their BTK gene, the gene defective in XLA, is normal. Several different genetic abnormalities have been described. Each of these abnormalities is inherited as an autosomal recessive trait (see chapter titled *Inheritance*). Therefore, both males and females can be affected with these deficiencies. These patients should be treated with immunoglobulin replacement therapy.

Antibody Deficiency with Normal or Elevated Immunoglobulins

These patients have severe infections similar to patients with Common Variable Immunodeficiency, but their immunoglobulin levels are normal or elevated. They have decreased antibody levels to most vaccine antigens, both protein and polysaccharide, which differentiate them from selective antibody deficiency patients.

Selective IgM Deficiency

These patients have low IgM (less than 30 mg/dl in adults, less than 20 mg/dl in children) with recurrent infections that are often severe. There are variable antibody responses. Some patients are asymptomatic. This disease may fit into the group of disorders called Common Variable Immunodeficiencies.

Selective IgE Deficiency

IgE is the allergy antibody. It is typically very low (< 5 IU/ml) in up to 10 percent of the patients attending an allergy clinic. Most of the patients are not ill, but recurrent respiratory infections have been described in some patients.

Immunodeficiency with Thymoma (Good's Syndrome)

This primary immunodeficiency is associated with a benign thymic tumor. Good's Syndrome is usually first suspected when a thymic tumor is seen on a chest X-ray. Most patients are adults. Removal of the thymic tumor does not cure the immunodeficiency although it may help other symptoms.

Antibody Deficiency with Transcobalamin II Deficiency

Transcobalamin 2 is a protein that transports vitamin B12 to the tissues from the gastrointestinal tract. A hereditary deficiency is associated with anemia, failure to thrive, low white cell counts and hypogammaglobulinemia. It can be treated with B12 injections.

Warts, Hypogammaglobulinemia, Infection, Myelokathexis (WHIM) Syndrome

WHIM is an autosomal recessive disorder (see chapter titled *Inheritance*) with severe warts, recurrent bacterial and viral infections and low, but not absent, immunoglobulins and neutropenia (low granulocytes). The latter is due to failure of the bone marrow to release granulocytes into the blood stream (myelokathexis). WHIM is caused by a defective gene for CXCR4, a chemokine protein that regulates leukocyte movement. Treatment includes immunoglobulin replacement therapy and G-CSF (see chapter titled *Specific Medical Therapy*).

Less Common Primary Cellular Immunodeficiencies

Drug-Induced Antibody Deficiency

Several pharmaceuticals may depress immunoglobulin and antibody levels, and this may result in recurrent infections. The chief drugs implicated include high-dose steroid drugs (particularly when given intravenously), anticonvulsant drugs (Dilantin and others), anti-inflammatory drugs used for arthritis, and the monoclonal antibody, Rituximab (Rituxan). The latter drug targets B-cells, the precursor of the antibody-producing plasma cells. In rare instances, severe and permanent hypogammaglobulinemia can occur with drug therapy, but usually the hypogammaglobulinemia reverses when the drug is discontinued.

Cellular immunodeficiencies discussed in previous chapters included severe combined immunodeficiency, ataxia telangiectasia, Wiskott-Aldrich syndrome and the DiGeorge syndrome. Some patients with less common cellular immunodeficiencies also have severe immunodeficiency with early onset and significant morbidity and mortality while others have mild problems. All have some defect of their T-cell (cellular) immune system, recognized by deep-seated infections, viral and fungal infections, and tuberculosis and other mycobacterial infections. Most of the other, less common T-cell deficiencies described below are relatively rare.

Chronic Mucocutaneous Candidiasis (CMC)

CMC is characterized by persistent *Candida* (fungus) infections of the mucous membranes, scalp, skin and nails, but not of the blood stream or internal organs (i.e. not systemic candidiasis). CMC is usually congenital and often hereditary, with onset in infancy manifested by persistent oral *Candida* infections (thrush). Later, the nails and skin become chronically infected. These infections respond to anti-*Candida* treatment but recur when the treatment stops.

CMC is associated with a selective T-cell deficiency to *Candida* and a few related fungi, but otherwise their immune system is fine. The most common abnormal laboratory test is a negative delayed hypersensitivity skin test to *Candida* antigen despite widespread *Candida* infection.

One hereditary form of CMC is the APECED Syndrome (autosomal recessive polyendocrinopathy-candidiasis-ectodermal dysplasia) associated with multiple endocrine problems (eg hypothyroidism or Addison disease) due to an AIRE gene defect on chromosome 21. A few CMC patients develop severe hepatitis or bronchiectasis. Treatment requires life-long antifungal medicines.

Cartilage Hair Hypoplasia (CHH)

CHH is an autosomal recessive immunodeficiency associated with dwarfism. It is particularly common among the Amish because of family intermarriage. Most patients have very fine brittle hair and an unusual susceptibility to viral infections. The immunodeficiency is variable and usually involves both antibody and cellular immunity. Some patients have been treated by bone marrow transplantation, but this will not correct their hereditary short stature.

X-linked Lymphoproliferative (XLP) Syndrome

XLP is characterized by life-long vulnerability to Epstein-Barr virus (EBV) infection, which can lead to severe and fatal infectious mononucleosis, lymph node cancers (lymphomas), combined immunodeficiency and, less commonly, aplastic anemia or vasculitis. XLP is associated with a defect on the X chromosome termed SH2DIA. This defect affects males. The mothers of the affected males and possibly some of their sisters are carriers (see chapter titled *Inheritance*).

Most XLP patients do well until they are exposed to EBV. Then, they become seriously ill with fever, swollen lymph nodes, enlarged liver and spleen, and hepatitis. If they recover, they go on to develop one of the above-named problems. Some patients are misdiagnosed with common variable immunodeficiency. Early recognition is crucial since the disease can be cured by bone marrow or cord blood transplantation. Immunoglobulin replacement therapy is often used, but this will not prevent the EBV infection.

Less Common Primary Cellular Immunodeficiencies continued

X-linked Immune Dysregulation with Polyendocrinopathy (IPEX) Syndrome

IPEX is characterized by multiple autoimmune endocrine diseases (particularly diabetes and thyroid problems), chronic diarrhea and a rash resembling eczema. IPEX is associated with abnormalities of a gene on the X chromosome termed FOXP3. These boys have activated T-cells which stimulate autoimmune problems. Early immunosuppressive medications (cyclosporin or tacrolimus) followed by bone marrow transplantation are commonly used as treatments.

Interferon- γ /IL-12 Pathway Deficiencies

These deficiencies are genetic disorders characterized by a special susceptibility to mycobacteria (the family of bacteria which cause tuberculosis and related infections) and salmonella infections. Many of the infants become ill as a result of a live BCG tuberculosis vaccination, given routinely at birth in many countries (not USA). Other patients have skin infections, swollen lymph nodes or blood stream infections with an enlarged liver and

spleen. The illness results from a genetic inability to make interferon and/or IL-12, two proteins that are especially important in helping to kill these bacteria within the white blood cells. Several genetic forms and several different molecular pathways are responsible. Treatment includes antibiotics and bone marrow transplantation.

Natural Killer Cell Deficiency

This is a rare disorder characterized by recurrent herpes virus infection and a selective deficiency of natural killer (NK) cells. Natural killer cells are lymphocytes (about 10 percent of the circulating lymphocytes) that are neither T- nor B-cells. Natural killer cells kill tumors and viral-infected cells and represent an early defense against cancer and viral infection. These patients may have recurrent or chronic herpes infections such as cold sores, severe Epstein-Barr virus infection, or varicella (chickenpox). Many of the patients require continuous anti-viral medicines.

Less Common Phagocytic Cell Deficiencies

The chief phagocytic white blood cell is the polymorphonuclear granulocyte (also known as neutrophil). To be effective, the neutrophil must move to a site of infection, ingest the organism and then kill the organism (see chapter titled *The Immune System and Primary Immunodeficiency Diseases*).

Neutropenias

Neutropenias are disorders characterized by low numbers of granulocytes, usually defined as a neutrophil count of less than 500 cells/ul (normal is more than 2000 cells/ul). Depending on its severity and duration, neutropenia can lead to serious and fatal infection or intermittent infection of the skin, mucus membranes, bones, lymph nodes, liver, spleen or blood stream (sepsis).

Neutropenia can occur at birth and can be life-long. One form, termed severe congenital neutropenia (Kostmann syndrome), is an autosomal recessive disorder. This disorder is associated with a gene abnormality of G-CSFR or the receptor for G-CSF, a cytokine that stimulates granulocyte growth. These infants require G-CSF and may have bone marrow transplantation. Another form of neutropenia is cyclic neutropenia which is an autosomal dominant disorder in which the neutropenia occurs every 2 to 4 weeks and lasts about a week. It is associated with a gene defect termed ELA-2.

A third form, benign chronic neutropenia, has low but not life-threatening neutropenia and is often asymptomatic. Treatment for all of these disorders may include antibiotics for infections, prophylactic antibiotics, G-CSF injections and bone marrow transplantation.

Less Common Phagocytic Cell Deficiencies continued

Several primary immunodeficiencies have an associated neutropenia. These immunodeficiencies include X-linked hyper-IgM syndrome, X-linked agammaglobulinemia, and WHIM syndrome. Some of these patients acquire an autoimmune antibody to their own neutrophils. This antibody causes neutropenia due to accelerated destruction of the neutrophils.

Phagocyte Killing Defects

Several rare phagocyte defects have an inability to kill organisms similar to patients with chronic granulomatous disease (CGD) (see chapter titled *Chronic Granulomatous Disease*). They should be suspected in patients who seem to have CGD but tests for that disorder are normal. These include enzyme defects or deficiencies of glucose-6-phosphate dehydrogenase, myeloperoxidase, glutathione reductase and glutathione synthetase.

Specific Granule Deficiency

Specific granule deficiency is associated with killing defects and decreased granules within their neutrophils.

Glycogen Storage Disease Type Ib

Glycogen storage disease type Ib is a disorder with neutropenia, poor granulocyte killing, a large liver and low blood sugar. It is due to a defect of the enzyme glucose-6 phosphate transporter 1 with accumulation of glycogen in the liver.

β -actin Deficiency

β -actin Deficiency is associated with poor granulocyte movement (chemotaxis) and recurrent infection. β -actin is a structural protein that allows cell movement. Some patients with chemotactic disorders have severe periodontitis and early tooth loss. Three of these syndromes are termed Papillon-Lefebvre syndrome, prepubertal periodontitis, and juvenile periodontitis.

Less Common Innate Immune Defects

Innate immunity includes those body defenses that are present at birth and do not increase following microbial exposure or immunization.

Toll-like Receptor (TLRs) Defects

Toll-like receptors are proteins present on the surface of many leukocytes that react with proteins present on many microbes. Upon contact with an organism these TLRs send internal messages to the nucleus of the cell to secrete cytokines, which stimulate the immune system, and kill invading microorganisms.

Several immunodeficiencies have been recently described in which cellular proteins that should transmit the message from the TLRs to the nucleus are abnormal, resulting in failure of cytokines to be produced in response to bacterial infection. One of these is a disorder termed IRAK-4 deficiency. Another is ectodermal dysplasia with immunodeficiency (EDA-ID), an X-linked disorder

associated with a defect of a gene termed NEMO which encodes an enzyme (IKK- γ) necessary for nuclear signaling (see chapter titled *Hyper IgM Syndrome*). Many of these latter patients have defects of sweating, sparse hair, abnormal dentition, and an antibody deficiency.

Mannose-binding Lectin (MBL) Deficiency

MLB is a deficiency of a circulating protein that allows microbes to activate the complement system. A hereditary deficiency of MBL is associated with recurrent severe infections. A partial deficiency may aggravate other problems such as cystic fibrosis, HIV or lupus erythematosus.