

Other Primary Cellular Immunodeficiencies



Chapter 14

Cellular immunodeficiencies (T-cell deficiency) discussed in previous chapters included Severe Combined Immune Deficiency (SCID), Ataxia-Telangiectasia, Wiskott-Aldrich Syndrome and DiGeorge Syndrome. Some patients with less common cellular immunodeficiencies may have severe immunodeficiency with early onset and significant morbidity and mortality while others have only mild problems. Patients with these types of deficiencies have some defect of their T-cell (cellular) immune system resulting in a different spectrum of infection problems than those individuals with typical antibody deficiency. These include deep-seated bacterial infections, viral and fungal infections, tuberculosis and other mycobacterial infections. Cellular immunodeficiencies are usually more difficult to treat and may need cellular reconstitution via hematopoietic stem cell transplantation or eventually perhaps gene therapy.

Chronic Mucocutaneous Candidiasis (CMC)

CMC is characterized by persistent *Candida* (fungus) infections of the mucous membranes, scalp, skin and nails. Rarely, the infection may spread to the blood stream or internal organs. CMC is usually hereditary and presents soon after birth with 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. Except for this T-cell deficiency, patients with CMC have a normally functioning immune system. The most common abnormal laboratory finding is a negative delayed hypersensitivity skin test to *Candida* antigen despite widespread *Candida* infection.

One hereditary form of CMC is the APECED Syndrome (autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia) associated with multiple endocrine problems (for example, hypothyroidism,

diabetes or Addison disease) due to an AIRE gene defect on chromosome 21. However, the CMC in this disease is also partly due to autoantibodies directed against critical *Candida* fighting molecules made by the disordered immune system. Several other forms of CMC are due to mutations in the gene signal transducer and activator of transcription 1 (STAT1). Other causes of CMC are associated with autoantibodies to critical *Candida* fighting molecules and with mutations in very uncommon genes such as interleukin 17. Treatment requires life-long antifungal medicines.

Cartilage Hair Hypoplasia (CHH)

CHH is an autosomal recessive immunodeficiency associated with dwarfism and other medical problems. 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 degree of 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.

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X-linked Lymphoproliferative (XLP) Syndromes 1 and 2

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 (inability to produce red blood cells) or vasculitis (inflammation in the blood vessels). XLP is associated with a defect on the X chromosome termed SH2DIA. As it is X-linked, this defect only affects males. (*See chapter titled “Inheritance.”*) Most patients with XLP do well until they are exposed to EBV. Then, they become seriously ill with fever, swollen lymph nodes, enlarged liver and spleen, and hepatitis. This infection triggers a condition called “hemophagocytic syndrome,” which also occurs in other immune deficiencies and can be fatal. If patients recover, they go on to develop one of the above-named problems.

Some patients are initially misdiagnosed with Common Variable Immune Deficiency (CVID). Early recognition is crucial since the disease can be cured by bone marrow or cord blood transplantation. Early screening of infant boys in families known to have had children with XLP is also critically important so that they can be transplanted before contracting an EBV infection. There are two forms of this disorder: XLP1 due to defects in the SH2DIA gene, and XLP2 due to defects in the XIAP gene.

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. It is an x-linked disease so only boys are affected. (*See chapter titled “Inheritance.”*) IPEX is caused by abnormalities of a gene on the X chromosome termed FOXP3. These boys have activated T-cells, which stimulate autoimmune problems. Immunosuppressive medications followed by bone marrow transplantation are commonly used as treatments.

Veno-occlusive Disease (VODI)

Hepatic veno-occlusive disease is an extremely rare form of immunodeficiency inherited in autosomal recessive fashion with impairment of both T-cells and B-cells. Patients with VODI have a predisposition to leaving the patient subject to fungal infections such as *Pneumocystis jiroveci* infection. Patients may also have thrombocytopenia (low platelet counts) and enlarged livers. Intravenous immunoglobulin (IVIG) and *Pneumocystis jiroveci* prophylaxis as soon as the diagnosis of VODI is established is important. Liver transplantation is sometimes considered, but the rate of complications may be high.

Hoyeraal-Hreidarsson Syndrome (Dyskeratosis Congenita)

This syndrome has X-linked inheritance, and patients have poor growth inside the womb, microcephaly (small head), pancytopenia (low numbers of all blood cells), and especially decreased natural killer cells. Patients experience a progressive loss of cellular and humoral immunity and are thus susceptible to infections by virtually any pathogen. Accurate diagnosis of Dyskeratosis Congenita is critical to ensure proper clinical management, because patients who have DC and bone marrow failure do not respond to immunosuppressive therapy and may have increased morbidity and mortality associated with hematopoietic stem cell transplantation.

Immunodeficiency with Centromeric Instability and Facial Anomalies (ICF)

ICF syndrome is a very rare disorder inherited from both parents due to defects in the DNA methyl transferable gene DNMT3B. Abnormal facial features are prominent such as macroglossia (large tongues). T-cell and B-cell numbers and serum immunoglobulins are all low and patients are susceptible to bacterial and opportunistic infections. Early diagnosis of ICF is important since early introduction of immunoglobulin supplementation can

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improve the course of the disease. Allogeneic stem cell transplantation should be considered as a therapeutic option in patients with severe infections or failure to thrive.

Schimke Syndrome

Schimke Syndrome is a very rare primary immunodeficiency with autosomal recessive inheritance that results in decreased circulating T-cells but normal levels of B-cells and serum immunoglobulins. Features associated with this syndrome are short stature, intrauterine growth retardation, kidney disease, bone marrow failure and problems fighting all types of infections. It is caused by a mutation in the gene responsible for chromatin remodeling (SMARCAL1). Additional features include ischemic cerebral attacks, migraine-like headaches, hematologic abnormalities of leucopenia, anemia and thrombocytopenia, enteropathy, hyper-pigmented skin macules, unusual hair and small teeth. The course of the disease varies from severe with intrauterine or early childhood onset and death in childhood to milder disease with survival into adulthood. For both severe and mild disease, the therapy is mainly symptomatic.

Comel-Netherton Syndrome

This is a very rare disorder with an autosomal recessive inheritance pattern. Patients have normal T-cell numbers but reduced numbers of B-cells. Patients exhibit increased IgE and IgA levels with variable-specific antibody function. Newborns exhibit ichthyosis (scaly skin), bamboo type hair (thin, tubular and fragile), an increased incidence of bacterial infections and growth failure. If antibody deficiency can be confirmed by vaccine challenge, immunoglobulin replacement could be tried.

In the neonatal period, 20% of the babies suffer from dehydration, electrolyte imbalances, perturbed thermoregulation, failure to thrive and recurrent infections which may result in early death. The hallmark of C-NS is trichorrhexis invaginata (bamboo hair), but other abnormalities, including pili torti (twisted hair) and trichorrhexis nodosa (hair of varying diameter) have been observed. Markedly elevated IgE levels, allergic reactions to food and common antigens, malnutrition, and increased susceptibility to skin, respiratory tract or systemic infections are also characteristic.