CHAPTER e39

Primary Immunodeficiencies Associated With (or Secondary to) Other Diseases

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There are an increasing number of conditions in which a primary immunodeficiency (PID) has been described as one facet of a more complex disease setting. It is essential to consider associated diseases when a PID is identified as the primary manifestation and, conversely, not neglect the potentially harmful consequences of a PID that could be masked by other manifestations of a particular syndrome.

Below is a short description of these syndromes in which the PID is classified according to the arm of the immune system that is affected.

1. **Primary immunodeficiencies of the innate immune system**
   - **a)** Several severe congenital neutropenia (SCN) syndromes can be associated with malformations. The recently described SCN disease caused by glucose-6-phosphatase deficiency (G6PC3) can be associated with heart and urogenital malformations. The related glycogenesis Ib disease combines SCN with hypoglycemia and hepatosplenomegaly. Some *HAX-1* gene mutations lead to neurocognitive impairments as well as SCN. Barth syndrome combines SCN with cardiomyopathy. Lastly, Shwachman syndrome is a known autosomal recessive entity (caused by mutation of the *SBDS* gene) in which the defect in granulopoiesis can extend to the other hematopoietic lineages; short stature, bone metaphyseal dysplasia, and exocrine pancreatic insufficiency are known hallmarks of this condition.
   - **b)** Syndromic asplenia combines the risk of infection with heart defects and situs inversus.
   - **c)** Leukocyte adhesion deficiency (LAD) type II includes growth retardation and impairment of cognitive development.
   - **d)** A few patients with X-linked chronic granulomatous disease present with a contiguous gene deletion syndrome that can include the McLeod phenotype, which is characterized by anemia, acanthocytosis, and a severe risk of immune reaction against donor red cells because the patient's red cells do not express the Kell antigen. The McLeod phenotype also can result in a neurologic disease.
   - **e)** X-linked NF-kappa-B essential modulator (NEMO) deficiency provokes not only a variable set of deficiencies of both innate and adaptive immunity but also mild osteopetrosis, lymphedema, and, more frequently, anhydrotic ectodermal dysplasia, dysmorphic facies, and abnormal conical teeth. The last finding is often helpful in the diagnosis of that condition.
2. **Primary immunodeficiencies of the adaptive immune system**
   - **a) T cell primary immunodeficiencies.** Reticular dysgenesis, a rare severe combined immunodeficiency (SCID) characterized by T lymphopenia and agranulocytosis, can cause sensorineural deafness. Coronin A deficiency is another SCID variant that can be associated with behavioral disorders because the Coronin A gene is located in a genome area known to have been deleted in some patients with this disorder. The lack of enzymes of purine metabolism (adenosine deaminase and purine nucleoside phosphorylase) provokes not only profound T cell lymphocytopenia but also neurologic impairment, including dysautonomia and abnormalities of cognitive development of variable intensity, in many patients. The neurologic impairment can persist after hematopoietic stem cell transplantation (HSCT). Mild chondrodysplasia is a common finding in adenosine deaminase (ADA) deficiency and, indeed, can help the physician arrive at a final diagnosis.
   - **b) Primary thymic defects.** DiGeorge syndrome is a complex embryopathy that is caused by hemizygous interstitial deletion of chromosome 22, leading to multiple developmental defects, including conotruncal defects, hypoparathyroidism, and dysmorphic syndrome. Although a profound T cell immunodeficiency is rare in DiGeorge syndrome (~1% of cases), failure to recognize this feature is likely to have a fatal outcome. Similarly, some forms of the related CHARGE syndrome (mutation of the *CHD7* gene) also cause a profound T cell immunodeficiency.
   - **c) T cell primary immunodeficiencies related to calcium influx defects.** Very recently, rare T cell PIDs were found to be caused by defective store-operated entry of calcium ions into T and B lymphocytes after antigen stimulation. These defects (caused by ORA-1 and STIM-1 deficiencies) also lead to anhydrotic ectodermal dysplasia, abnormal teeth, and, above all, a nonprogressive muscle disease characterized by excessive fatigue.
   - **d) DNA repair defects.** Several genetic defects impair DNA repair pathways. Many lead to combined T and B lymphocyte PIDs in a syndromal setting of varying complexity. The most common is ataxia telangiectasia (AT), an autosomal recessive disorder with an incidence of 1 in 40,000 live births; AT causes a B cell immunodeficiency (low IgA, IgG2 deficiency, and low antibody production) that often requires immunoglobulin replacement therapy.

     AT is associated with a progressive T cell immunodeficiency. As the condition's name suggests, the hallmark features are telangiectasia and cerebellar ataxia.

     These manifestations may not be detectable before age 3–4 years, and so AT should be considered in young children with IgA deficiency and problematic infections. Diagnosis is based on a cytogenetic analysis showing excessive chromosomal rearrangements (mostly affecting chromosomes 7 and 14) in lymphocytes. AT is caused by mutation of the gene encoding the ATM protein, a kinase that plays a major role in the detection of DNA lesions and the organization of DNA repair (or cell death if the lesions are too numerous) by triggering several different pathways. Overall, AT is a progressive disease that carries a very high risk of lymphoma, leukemia, and (during adulthood) carcinomas. A variant of AT (AT-like disease) is caused by mutation of the *MRE11* gene.

     Nijmegen breakage syndrome (NBS) is a less common condition that also results from chromosome instability (and the same cytogenetic abnormalities as in AT). It is characterized by a severe T and B cell combined immunodeficiency with autosomal recessive inheritance. Subjects with NBS exhibit microcephaly and a birdlike face but neither ataxia

nor telangiectasia. The risk of malignancies is also very high. Nijmegen breakage syndrome results from a deficiency in Nibrin (NBS1, a protein associated with MRE11 and Rad50 that is involved in checking DNA lesions) caused by hypomorphic mutations.

Severe forms of dyskeratosis congenita (also known as Hoyeraal-Hreidersson syndrome) combine a progressive immunodeficiency that can include an absence of B and natural killer cell (NK) lymphocytes, progressive bone marrow failure, microcephaly, in utero growth retardation, and gut disease. The disease can be X-linked or, more rarely, autosomal recessive. It is caused by the mutation of genes encoding telomere maintenance proteins, including dyskerin (DKC1).

Bloom syndrome (helicase deficiency) combines a typical dysmorphic syndrome with growth retardation, skin lesions, and a mild immunodeficiency that also can be found in some patients with Fanconi's anemia.

Rare forms of combined T and B cell immunodeficiencies with autosomal recessive inheritance are associated in more complex syndromes with microcephaly, failure to grow, and a variable dysmorphic syndrome. These disorders are caused by mutation of the genes that encode DNA ligase 4 and Cernunnos (XLF), both of which are members of the nonhomologous end-joining DNA repair pathway.

Lastly, immunodeficiency, centromere instability, and facial anomalies (ICF) syndrome is a complex autosomal recessive syndrome that variably combines a mild T cell immunodeficiency and a more severe B cell immunodeficiency with a coarse face, intestinal disease, and mild mental retardation. A cytogenetic diagnostic feature is the presence of multiradial chromosomes (most frequently chromosomes 1, 9, and 16) caused by DNA defective methylation. The syndrome is a result of DNA methyltransferase DNMT3B deficiency.

e) **Growth hormone insensitivity syndrome (Laron dwarfism) with combined primary immunodeficiency.** Mutations in the *STAT5b* gene, which encodes a transcription factor involved in signaling downstream of the growth hormone receptor and the interleukin 2 (IL-2) receptor, lead to susceptibility to infection because of a partial, functional T cell immunodeficiency associated with autoimmune manifestations. The autoimmune manifestations probably result from defective generation/activation of regulatory T cells.

f) **Hyper-IgE syndrome (autosomal dominant form).** Hyper-IgE syndrome is a complex disorder that combines skin infections, inflammation, and susceptibility to bacterial and fungal infections of skin and lungs, often with pneumatoceles, with characteristic syndromic signs such as facial dysmorphy, defective loss of primary teeth, hyperextensibility, scoliosis, and osteoporosis. Elevated serum IgE levels are typical of hyper-IgE syndrome. The recently reported defects in TH17 effector responses account, at least in part, for the vulnerability to specific infections. This condition is caused by heterozygous (dominant) mutation of the gene encoding the transcription factor STAT3, which is required in a number of signaling pathways downstream of cytokine/cytokine receptor interactions (notably for IL-6).

g) **Primary immunodeficiencies with bone disease.** The autosomal recessive cartilage hair hypoplasia (CHH) disease is characterized by short-limb dwarfism, metaphyseal dysostosis, and sparse hair, together with a combined T and B cell PID of variable intensity, ranging from quasi-SCID to an absence of clinically significant immunodeficiency. The condition can predispose to erythroblastopenia, autoimmunity, and tumors. It is caused by mutations in the *RMRP* gene for a noncoding ribosome-associated RNA.

Schimke immunoosseous dysplasia is a rare autosomal recessive condition characterized by severe T and B cell immunodeficiency with spondyloepiphyseal dysplasia, growth retardation, and kidney and vascular diseases. It is the consequence of mutations in the *SMARCAL1* gene. The function of the gene product may be related to DNA repair.

h) **Venoocclusive disease with immunodeficiency (VODI syndrome)** is a rare autosomal recessive condition predominantly found in populations originating from Lebanon. It combines severe hepatic venoocclusive disease with usually mild T cell immunodeficiency and panhypogammaglobulinemia. It is caused by a deficiency in a nuclear protein, Sp110.

3. **B cell primary immunodeficiencies**
Hypogammaglobulinemia can be associated with chromosomal defects such as trisomy 18 and Jacobsen syndrome (hemizygous deletion of part of the long arm of chromosome 11). A rare biallelic deficiency of the mismatch repair protein PMS2 leads to a partial deficiency in Ig class switch recombination in patients at a very high risk of cancer in general and colon carcinomas and lymphomas in particular. Transcobalamine deficiency disturbs vitamin B_{12} transport and therefore impairs hematopoiesis. Hypogammaglobulinemia is easily corrected by vitamin B_{12} administration and can be a characteristic of this very rare disorder.

4. **Primary immunodeficiencies affecting regulatory pathways**
Several inherited disorders that lead to hemophagocytic lymphohistiocytosis (HLH) also have features that are important in terms of both diagnosis and prognosis. Three of these disorders—Griscelli syndrome, Chédiak-Higashi syndrome, and the Hermansky-Pudlak type II syndrome—are characterized by partial albinism and silvery hair appearance that can facilitate diagnosis. Hermansky-Pudlak type II also can be a bleeding disorder if platelet aggregation is defective. Chediak-Higashi syndrome also is characterized by an early-onset progressive neurologic disorder with impaired cognitive development and motor and sensory deficiencies, culminating in a generalized encephalopathy. The encephalopathy is not prevented or arrested by allogeneic HSCT even when the HLH risk is controlled.

5. **Primary immunodeficiencies associated with other conditions**
A number of conditions can cause PIDs indirectly. For example, hypercatabolism in patients with Steinert's disease may cause hypogammaglobulinemia. Intestinal lymphangiectasia that includes both immunoglobulin and naive T cell loss and can expose the patient to a significant infectious risk. Urinary IgG loss may result from severe nephritic syndromes.

A number of drugs, including antimalarials, captopril, penicillamine, phenytoin, and sulfazaline, can induce predominantly IgA hypogammaglobulinemia in (probably predisposed) adults.

One also should also consider (1) diseases that are not thought to be PIDs but include the occurrence of recurrent infections and (2) genetic defects of the immune system that lead to other clinical manifestations. A very good example of the first group is cystic fibrosis (CF). Despite having a functionally normal immune system, patients with CF develop protracted bacterial respiratory tract infections, notably *Pseudomonas aeruginosa* colonization. This bacterium can incapacitate innate immune responses and cause unremitting inflammation that further facilitates infection. An example of the second group is primary alveolar proteinosis, which is caused by a defect in surfactant clearance by alveolar macrophages. The condition results from mutation of the gene encoding the granulocyte-macrophage colony-stimulating factor receptor α.