Immunodeficiency Disorders

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Education Gaps

Immunodeficiencies are no longer considered rare conditions. Although susceptibility to infections has become well-recognized as a sign of most primary immunodeficiencies, some children will present with noninfectious manifestations that remain underappreciated and warrant evaluation by an immunologic specialist. Providers must also consider common secondary causes of immunodeficiency in children.

Objectives After completing this article, readers should be able to:

1. Recognize infectious signs and symptoms of primary immunodeficiency that warrant screening and referral to a specialist.
2. Understand noninfectious signs and symptoms that should raise concern for primary immunodeficiency.
3. Determine appropriate testing for patients for whom immunodeficiency is suspected.
4. Discuss the management of patients with primary immunodeficiency.
5. Appreciate secondary causes of immunodeficiency.

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ABBREVIATIONS
ALC absolute lymphocyte count
ALPS autoimmune lymphoproliferative syndrome
CGD chronic granulomatous disease
HIV human immunodeficiency virus
HLH hemophagocytic lymphohistiocytosis
Ig immunoglobulin
PID primary immunodeficiency
SCID severe combined immunodeficiency disease
SLE systemic lupus erythematosus
TLR toll-like receptor

INTRODUCTION

Immunodeficiency disorders represent defects in the immune system that result in weakened or dysregulated immune defense. These deficiencies may occur as primary diseases or secondary conditions. This article reviews primary and secondary immunodeficiencies, with particular emphasis on the evaluation and management of children with primary immunodeficiencies (PIDs).

PRIMARY IMMUNODEFICIENCIES

PIDs constitute inherent defects in immunity, most of which arise from inborn deviations in the genetic code. More than 300 PIDs have been identified. These conditions have been placed into 9 categories corresponding with their clinical and immunologic phenotypes by an international group of experts who evaluate these diseases every 2 years (Table 1). (1) Although PIDs were previously believed

TABLE 1. **Primary Immunodeficiency Categories (1)**

1. Immunodeficiencies affecting cellular and humoral immunity
2. Combined immunodeficiencies with associated or syndromic features
3. Predominantly antibody deficiencies
4. Diseases of immune dysregulation
5. Congenital phagocytic defects
6. Defects in intrinsic and innate immunity
7. Autoinflammatory disorders
8. Complement deficiencies
9. Phenocopies of PIDs

to represent rare conditions, they are now known to affect 1 of every 1,200 to 2,000 individuals, with growing prevalence due to increased recognition. (2)(3) The magnitude of this disease frequency, therefore, mandates that all healthcare providers recognize the associated clinical infectious and noninfectious characteristics, testing options, and management recommendations for children with PIDs. And because so many PIDs present in childhood, and several are now captured by newborn screening, their understanding by pediatricians remains especially important.

Infectious Signs and Symptoms of PID

Infections serve as the key hallmark warning signs for the presence of PID. (4) In general, children with PIDs develop infections more frequently, more severely, and more atypically. Although noninfectious characteristics of PIDs can result from inappropriate immune function and are discussed in the next section, the link between PID and infection remains essential and must be regarded as a prompt to consider PID in pediatric practice. Each of the 9 PID categories conveys a different risk for certain infectious susceptibilities in accordance with the molecular mechanism for the impaired immunity. Offending organisms encompass the entire spectrum of pathogens, including bacteria, viruses, fungi, and parasites. Thus, awareness of infections associated with defective humoral immunity, T-cell function, phagocytic capacity, complement activity, and other innate immunity becomes essential.

Defects in humoral immunity that cause PID result in impaired antibody production. Infants receive maternal immunoglobulin (Ig) G transplacentally. Because the half-life of IgG is approximately 21 days in the circulation, children have protection from these maternal antibodies until approximately 3 to 4 months of life. At that time, characteristic infections tend to ensue, although some antibody deficiencies are known to present at older ages. Because antibodies serve as critical elements for protection of the sinopulmonary tract, affected individuals typically develop recurrent otitis media, sinusitis, and pneumonia. Infections are by no means limited to these sites, however, and can result in sepsis, meningitis, osteomyelitis, or chronic diarrhea. For example, X-linked agammaglobulinemia is characterized by a lack of B cells due to mutations in *BTK* located at Xq22.1. Absence of B cells results in failure to produce IgG, IgA, IgM, and IgE. In affected boys, disappearance of maternal antibodies is associated with the appearance of recurrent sinopulmonary tract infections, classically by polysaccharide-encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. (5) The lack of antibodies also results in susceptibility to infections by mycoplasmal and pseudomonal organisms, *Salmonella* species, *Campylobacter jejuni*, rotavirus, and *Giardia lamblia*.

T-cell deficiency produces combined humoral and cellular immune defects. Because of this extensive effect on immune function, affected individuals demonstrate susceptibility to opportunistic fungal, viral, mycobacterial, and parasitic infections in addition to the infections observed in antibody deficiencies. Classic pathogens include candidal species, *Pneumocystis jirovecii*, *Mycobacteria* species (including bacille Calmette-Guérin), and *Cryptosporidium parvum*. Viral infections surpass the ordinary and are notably severe, disseminated, or persistent. Severe combined immunodeficiency disease (SCID) serves as a classic example of primary T-cell deficiency. The diagnosis is established by either 1) the absence or a very low number of T cells (<300 $CD3^+$ T cells/mm^3) with no or very low T-cell function (<10% of the lower limit of normal) as determined by response to phytohemagglutinin or 2) the presence of T cells of maternal origin. (6) Mutations in at least 16 genes lead to SCID, and most forms are caused by disrupted T-cell development secondary to abrogated T-cell receptor formation or cytokine signaling (Table 2). (1) The most common type of SCID in the United States results from mutations in *IL2RG* at Xq13.1 and is, thus, found in boys. SCID represents a true pediatric emergency, and mortality from infections is certain if affected infants are not treated appropriately. (7) Life-threatening infections are caused by respiratory syncytial virus, rhinovirus, parainfluenza virus, adenovirus, cytomegalovirus, and even attenuated vaccine strains of measles virus, varicella virus, rotavirus, and oral poliovirus. Invasive bacterial and fungal infections also occur, the former mostly resulting from impaired humoral immunity secondary to the defects in T-cell immunity.

TABLE 2. **Causes of Severe Combined Immunodeficiency Disease**

ASSOCIATED GENE	LYMPHOCYTE PHENOTYPE	DEFECTIVE MECHANISM
IL2RG	$T^-B^+NK^-$	Signaling for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21
JAK3	$T^-B^+NK^-$	Same as *IL2RG*
RAG1	$T^-B^-NK^+$	Formation of T- and B-cell receptors
RAG2	$T^-B^-NK^+$	Same as *RAG1*
DCLRE1C	$T^-B^-NK^+$	Same as *RAG1*
PRKDC	$T^-B^-NK^+$	Same as *RAG1*
LIG4	$T^-B^-NK^+$	Same as *RAG1*
NHEJ1	$T^-B^-NK^+$	Same as *RAG1*
IL7R	$T^-B^+NK^+$	Signaling for IL-7
PTPRC	$T^-B^+NK^+$	Receptor signaling and T-cell activation
CD3D	$T^-B^+NK^+$	T-cell receptor signaling
CD3E	$T^-B^+NK^+$	Same as *CD3D*
CD247	$T^-B^+NK^+$	Same as *CD3D*
CORO1A	$T^-B^+NK^+$	Same as *CD3D*
AK2	$T^-B^-NK^-$	Stem cell maturation
ADA	$T^-B^-NK^-$	Lymphocyte survival

IL=interleukin.

Because neutrophils play a significant role in the clearance of bacterial and fungal pathogens, PIDs due to defective phagocytic capacity are marked by infections caused by these organisms. Phagocytic impairment can result from inadequate neutrophil quantity or function. Classic infections in children with neutrophil deficiency include skin or solid organ abscesses, cellulitis, pneumonia, sepsis, and severe gingivitis or periodontitis. Other signs of a phagocytic defect include omphalitis, poor wound healing, and aphthous stomatitis. Affected individuals have an increased risk of life-threatening infections from *Staphylococcus aureus* and *Pseudomonas aeruginosa*. As a key illustration, chronic granulomatous disease (CGD) serves as an example of PID caused by impaired neutrophil function. This condition arises from defects in components of nicotinamide adenine dinucleotide phosphate oxidase, which produces the oxidative burst needed for neutrophils to kill phagocytized organisms. (8) The most common form of CGD results from mutations in *CYBB*, which is located at Xp21.1-p11.4. Thus, most children with CGD are boys. CGD can be recognized by susceptibility to catalase-positive organisms, such as *S aureus*, *Serratia marcescens*, *Klebsiella* species, *Burkholderia cepacia*, *Aspergillus* species, and *Nocardia* species (8)(9) Infections caused by unusual pathogens, especially methylotrophic microorganisms capable of using single-carbon compounds as their sole source of energy, should also raise concern for the presence of CGD. (10) In children with CGD who have received bacille Calmette-Guérin immunization, infection by the bacterium itself should be considered. Characteristic sites of various infections in CGD include the skin, lungs, lymph nodes, liver, spleen, central nervous system, and bones.

Children with defects in primary complement deficiencies can be recognized by infections caused by encapsulated bacteria. (11) Complement deficiency, whether of the early or terminal classical complement pathway components, should be considered in children who have invasive meningococcal disease, such as sepsis or meningitis from *Neisseria meningitidis*. Individuals who have primary early classical complement pathway protein (C1, C4, C2, and C3) deficiencies further demonstrate susceptibility to other encapsulated bacteria, such as *S pneumoniae* and *H influenzae*.

Finally, children with PIDs due to other defects in innate immunity exhibit susceptibility to a variety of pathogens, depending on the critical defense mechanism affected. For example, natural killer cell deficiency should be suspected in

individuals with recurrent, unusual, or severe herpesviral infections. (12)(13) Children with defects in the interferon-γ–interleukin-12 signaling pathway, on the other hand, develop atypical mycobacterial infections. (14) Perturbation of other key innate immune signaling pathways leads to chronic mucocutaneous candidiasis, which should be suspected in children with thrush that is unusually recurrent or unresponsive to nystatin. (15) Finally, defects in toll-like receptor (TLR) signaling pathways offer an excellent example of the diversity of infectious susceptibilities affected by various innate immunity disorders. Humans express 10 TLRs, each of which performs an inherent danger-sensing function by recognizing specific intracellular or extracellular bacterial, fungal, or viral components. TLR3 deficiency leads to susceptibility to herpes simplex virus encephalitis. (16) IRAK-4 and MyD88, however, serve as adaptor molecules that mediate signaling downstream from all the other TLRs (except partly TLR4). Deficiencies of either of these proteins result instead in vulnerability to invasive infections (sepsis, meningitis, arthritis, and osteomyelitis, among others) that are caused by pyogenic bacteria, such as *S aureus*, *S pneumoniae*, and *H influenzae*, rather than by viruses or fungi. (17)

Noninfectious Signs and Symptoms of PID

Improved understanding of PIDs and enhanced diagnostic capabilities, especially genetic testing, (18) have provided greater awareness of the need to appreciate noninfectious manifestations, as discussed in the following paragraphs, that can serve as early or initial warning signs for the presence of underlying PID. The pediatrician should keep in mind that inherently defective immunity not only results in an inability to defend against the external environment (ie, infections) but also produces impaired ability to navigate the internal environment, leading to autoimmune and autoinflammatory conditions. In some children, these conditions will appear before infections ensue and can engage nearly any organ system. Affected children may, therefore, first come to the attention of other specialist providers. Presence of any of these features in a pediatric patient, especially with early or very early onset, should prompt consideration of additional evaluation for underlying PID. These noninfectious manifestations of PIDs are reviewed in the following accompanying tables and figures. Of importance, the lists of defective PID genes provided in the tables and figures are by no means comprehensive. Instead, they are intended to underscore the degree to which concern for PID is deserved.

Gastrointestinal disorders can reveal the presence of underlying PID (Table 3). (19) Autoimmune enteropathy can be observed when children lack regulatory T cells. The autoimmune disease in other PIDs, on the other hand, leads to inflammatory bowel disease. In several PIDs, dysregulated inflammation rather than autoimmunity results in inflammatory bowel disease. Finally, the presence of intestinal inflammation with bowel atresias is nearly uniquely associated with *TTC7A* deficiency. Thus, children with chronic enteropathy, inflammatory bowel disease, or multiple intestinal atresias should all be considered for evaluation for underlying PID.

A variety of dermatologic conditions, many of which relate to underlying dysregulated immunity in the skin, can signal the existence of PID (Fig 1). (20) Eczema is a presenting feature of several PIDs, most notably hyper-IgE syndrome and Wiskott-Aldrich syndrome. Neutrophilic pustular dermatosis, or Sweet syndrome, can be observed in proteasome-associated autoinflammatory syndromes. (21) Ectodermal dysplasia, on the other hand, can suggest PID due to a defect in nuclear factor kappa-light-chain-enhancer of activated B cells signaling or store-operated calcium entry. Cutaneous granulomas have been associated with CGD, ataxia-telangiectasia, and Blau syndrome in addition to several other PIDs. Abnormal hair can also serve as a sign of PID. Hypopigmented hair is observed in Chédiak-Higashi, Griscelli, and Hermansky-Pudlak syndromes, and thin or sparse hair is present in cartilage-hair hypoplasia and dyskeratosis congenita. Brittle hair due to trichorrhexis invaginata, so-called bamboo hair, is essentially pathognomic for Comèl-Netherton syndrome. Meanwhile, the complete absence of hair (alopecia totalis) should engender concern for *NFKB2* or *FOXN1* deficiency. Familial cold autoinflammatory syndrome is marked by a phenotype of cold-induced urticaria (as characterized by a wheal and flare response to an ice cube placed on the skin) and is caused by mutations in

TABLE 3. **Gastrointestinal Manifestations of PIDs**

NEARLY 40 PID GENES ARE ASSOCIATED WITH INFLAMMATORY BOWEL DISEASE OR NONINFECTIOUS ENTEROPATHY
ADAM17, AIRE, ARPC1B, BACH2, CD40LG, CD55, CTLA4, CYBA, CYBB, DKC1, DOCK8, FOXP3, IKBKG, IL10, IL10RA, IL10RB, IL2RA, ITCH, LRBA, MALT1, MVK, NCF1, NCF2, NCF4, NEIL3, NFAT5, NLRC4, NOD2, PIK3CD, PLCG2, STAT1, STAT3, STXBP2, TNFAIP3, TTC37, TTC7A, WAS, XIAP, ZBTB24

PID=primary immunodeficiency.

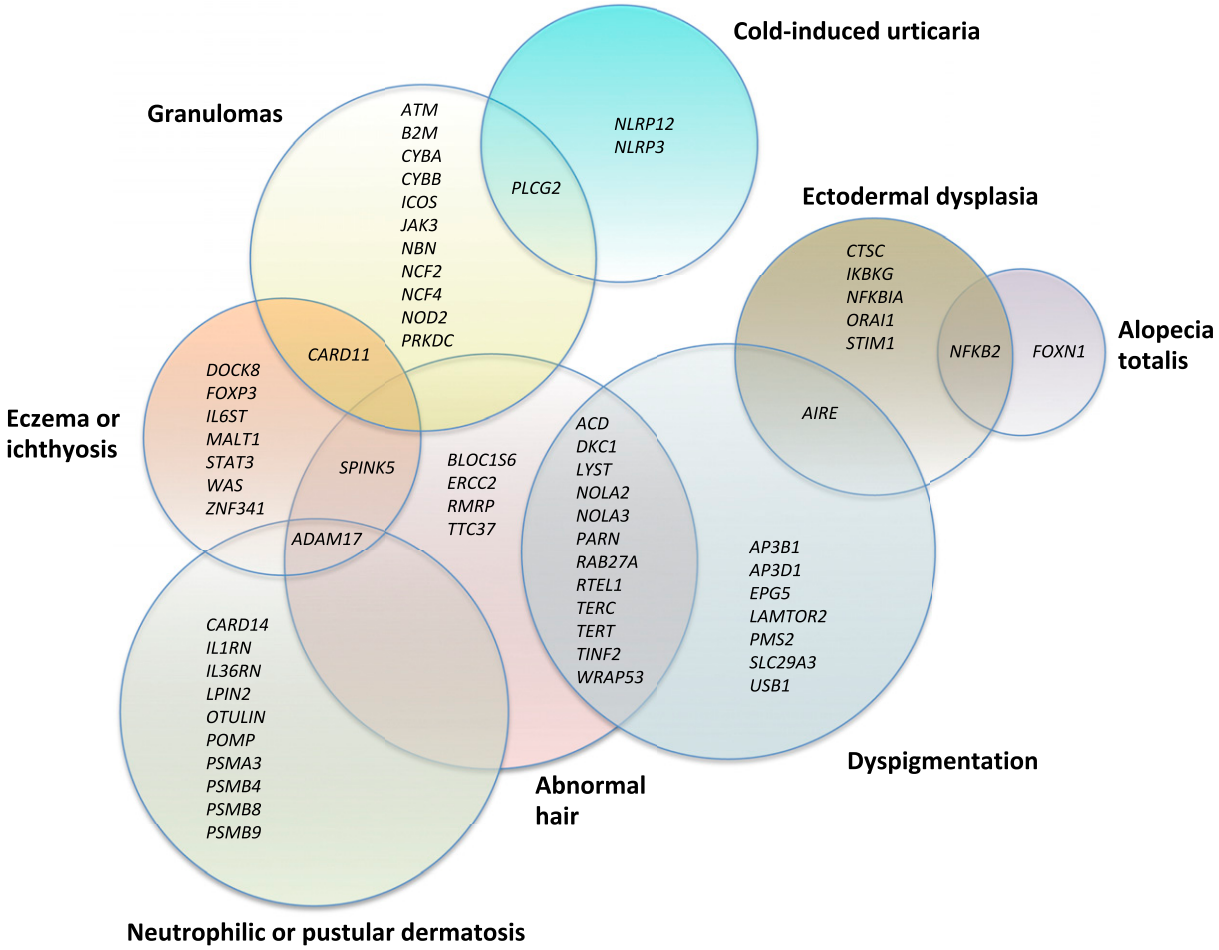


Figure 1. Dermatologic manifestations of primary immunodeficiencies.

NLRP3 or *NLRP12*. A different form of cold-induced urticaria that produces a negative ice cube test but significant wheal responses to evaporative cooling occurs in PLCγ2-associated antibody deficiency and immune dysregulation. Finally, abnormal skin pigmentation can be found in several PIDs, including dyskeratosis congenita (reticular hyperpigmentation) and Chédiak-Higashi, Griscelli, or Hermansky-Pudlak syndromes (hypomelanosis or albinism).

Because PIDs are caused by deficient and dysregulated immunity, it comes as little surprise that some affected individuals will present with autoimmune disease as the chief or even sole manifestation (Fig 2). (22)(23)(24) Noninfectious arthritis, including juvenile idiopathic arthritis, may be a sign of a hyperinflammatory PID condition. Autoimmune cytopenias are classically associated with impaired immunologic tolerance, whether through defective negative selection of T cells in the thymus or decreased regulatory T-cell inhibition of autoreactive T cells. (25) They can also present in individuals with autoimmune lymphoproliferative syndrome (ALPS). Vasculitis serves as a feature of many of the periodic fever syndromes and several complement deficiencies. In terms of periodic fever syndromes, the known associated features underscore the need to consider further evaluation in a child who develops fevers of regular chronicity, arthritis, or vasculitis, and any other signs of inflammation. Most of these syndromes result from hyperactivation of inflammasomes, which are protein complexes critical for inducing inflammatory responses, and can be treated with targeted biological modifiers. (26) Vasculitic disease is also known to occur in several newly described PIDs. Thus, it seems likely that novel PIDs will continue to be discovered as causes of vasculitis in children. Finally, evaluation for PIDs should be considered for children who present with systemic lupus erythematosus (SLE) or SLE-like disease. SLE is known to be associated with deficiencies of almost all components of the classical complement pathway (except C9). Individuals with CGD and ALPS can also present with SLE-like features. It remains important to note that variants of the disease known as hemophagocytic lymphohistiocytosis (HLH) can present with an

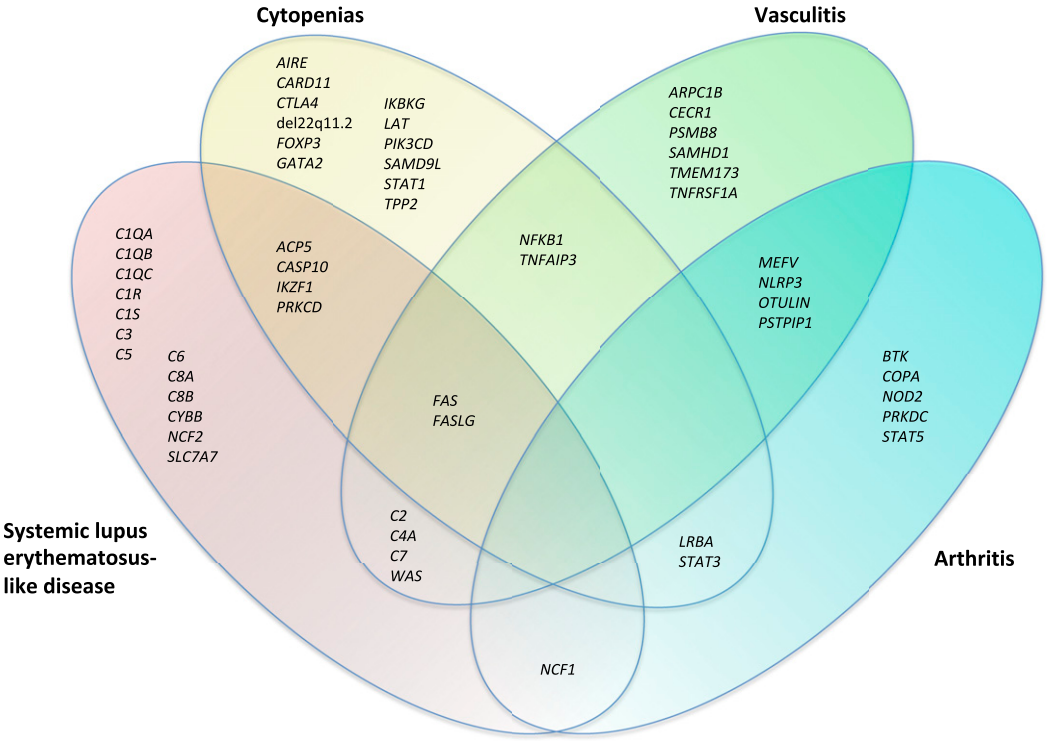


Figure 2. Autoimmune manifestations of primary immunodeficiencies.

inflammatory syndrome known as macrophage activation syndrome. This condition must be recognized appropriately because it is treated more like HLH than other inflammatory conditions that the symptoms might mimic.

Screening for PIDs should be strongly considered in children with early-onset endocrinopathies (Fig 3). Most of these endocrine disorders are autoimmune, resulting from the disrupted tolerance mechanisms inherent to the associated PIDs. Severe or difficult-to-control type 1 diabetes can indicate regulatory T-cell dysfunction. Primary adrenal insufficiency is an archetypal feature of *AIRE*, *MCM4*, and *NFKB2* deficiencies. Hypoparathyroidism is observed in *AIRE* deficiency and DiGeorge anomaly. In fact, the association between neonatal hypocalcemia and DiGeorge anomaly remains well appreciated. Clinicians must realize that the absence of 22q11.2 hemizygosity does not exclude the diagnosis of DiGeorge anomaly, as nearly half of affected individuals may not have the characteristic deletion. (27) Children who present with any features (eg, hypocalcemia or hypoparathyroidism, congenital cardiac disease, or developmental or neuroanatomical defects) characteristic of DiGeorge anomaly should, therefore, be evaluated for potential thymic dysfunction. Growth hormone deficiency represents a classic characteristic of *STAT5B* deficiency but is additionally known to occur in patients with *NFKB2* deficiency and ataxia-telangiectasia. Finally, thyroid disease seems underappreciated as a manifestation of PID but can provide a clue to the existence of underlying PIDs.

Two important hematologic/oncologic conditions should raise concern for underlying PIDs (Table 4). The PID mechanisms that lead to these 2 disorders include impaired control of immunologic activation and dysregulated proliferation of immune cells. First, lymphoproliferative disease suggests an inherent defect in immune function. For example, in ALPS, abnormal proliferation of immune cells occurs due to defective apoptosis. Meanwhile, several other PIDs are characterized by lymphoproliferative disease associated with Epstein-Barr virus infection. Lymphoid hyperplasia is observed in autosomal recessive hyper-IgM syndromes. Second, pediatric patients who develop HLH should be screened for PIDs if they do not have defects in any of the familial HLH genes. (28)(29) PIDs associated with HLH include Chédiak-Higashi, Griscelli, and Hermansky-Pudlak syndromes; CGD; periodic fever syndromes; and a variety of other conditions that affect cytotoxic T-cell or natural killer cell function.

Several PIDs are characterized by neurologic signs (Fig 4). (30) These abnormalities occur most typically due to roles that the damaged genes would normally serve outside of the immune system. That said, the precise mechanism for ataxia and hearing loss remains unclear in many conditions and is often not directly related to the defective

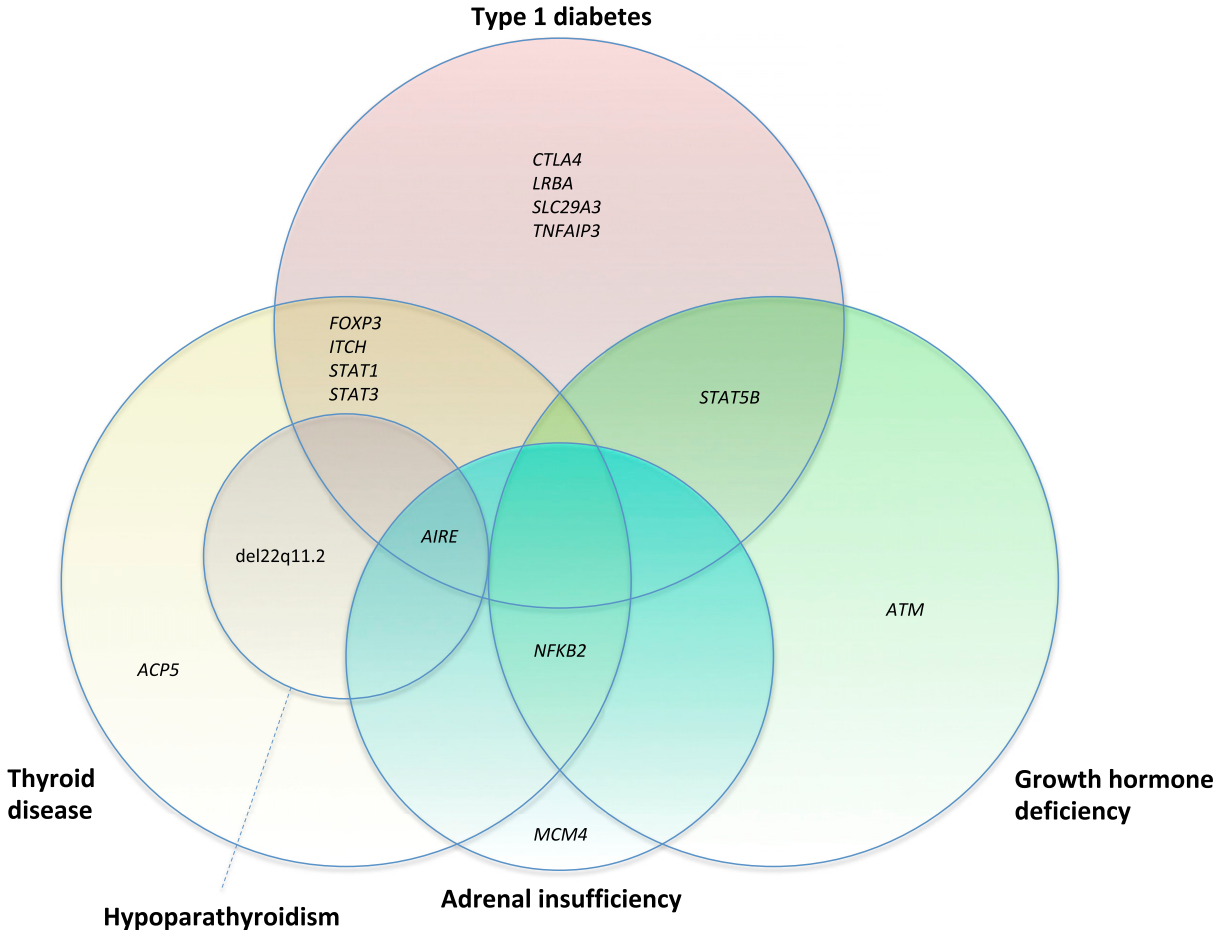


Figure 3. Endocrinologic manifestations of primary immunodeficiencies.

immune function in the associated PID. Ataxia is a typical feature of ataxia-telangiectasia, Chédiak-Higashi syndrome, and Hoyeraal-Hreidarsson syndrome, among others. Hearing loss, on the other hand, is a fundamental attribute of Carnevale-Mingarelli-Malpuech-Michels syndrome, Muckle-Wells syndrome, H syndrome, and other PIDs. Next, developmental delay is clearly associated with a variety of PIDs, but providers often neglect to evaluate for defective immunity due to the attention given to the neurologic deficits. This association emphasizes the critical intersection between neurologic development and activity and immune function, especially in terms of preservation of DNA integrity. Double-stranded break DNA repair seems to play an essential role in cognitive development, and children with PIDs caused by a defect in this repair mechanism present with developmental delay. As another example, developmental delay is observed in immunodeficiency–centromeric instability–facial anomalies syndrome, which is caused by aberrant

TABLE 4. **Hematologic/Oncologic Manifestations of PIDs**

CONDITION	ASSOCIATED PID GENES
Lymphoid hyperplasia or lymphoproliferative disease	*AICDA, CASP8, CASP10, CD27, CD70, CECR1, CTLA4, FAAP24, FAS, FASLG, ITK, LAT, LRBA, MAGT1, MVK, PIK3CD, PIK3R1, PRKCD, RASGRP1, RBCK1, SH2D1A, SLC29A3, STAT3, STAT5B, STK4, TPP2, UNG, XIAP*
Hemophagocytic lymphohistiocytosis	*AP3B1, ATM, BTK, CARMIL2, CD27, CD3E, CYBA, CYBB,* del22q11.2, *DKC1, FAS, IKBKG, IL2RG, IL7R, ITK, LYST, MAGT1, MEFV, NCF1, NLRC4, ORAI1, PIK3CD, PRF1, RAB27A, RAG1, RAG2, SH2D1A, STAT1, STAT2, STAT3, STX11, STXBP2, TNFRSF1A, UNC13D, WAS, XIAP*

PID=primary immunodeficiency.

DNA methylation and chromatin structure. Other examples of developmental delay and PID caused by inappropriate processing of nucleic acids include *ADAR*, *CHD7*, *SMARCAL1*, and *TRNT1* deficiencies. Aside from defects in nucleic acid handling, glycosylation is also known to play a vital role in immunologic and neurologic processes. As a result, a variety of congenital disorders of glycosylation represent PIDs that manifest as developmental delay. Last, unidentified DiGeorge anomaly should always be considered in a child with neurocognitive deficits, behavioral issues, or various psychiatric disorders. (31) Thus, clinicians should be aware of these neurologic associations and consider immunologic evaluation accordingly.

Several rare noninfectious pulmonologic conditions can suggest the presence of underlying PIDs (Table 5). Interstitial lung disease has been reported in several PIDs. Pulmonary alveolar proteinosis is most commonly associated with *CSF2RA* deficiency but can also be observed in patients with other PIDs. Pulmonary capillaritis and hemorrhage should raise concern for *COPA* syndrome. Finally, eosinophilic pneumonia represents a key feature of lung disease, immunodeficiency, and chromosome breakage syndrome caused by *NSMCE3* deficiency.

Finally, clinicians should be aware of 2 additional noninfectious manifestations of PIDs (Table 6). First, allergies, which are often severe or directed toward numerous agents, can serve as the presenting feature of several PIDs. In many of these conditions, the atopy is accompanied by markedly elevated serum IgE levels. Second, skeletal dysplasia serves as a classic feature of spondyloenchondrodysplasia with immune dysregulation, cartilage-hair hypoplasia, and Schimke immuno-osseous dysplasia but can denote the presence of other PIDs as well.

When to Test for PID

The decision of when to test for or refer a child for evaluation of a suspected PID may be affected by several factors.

First, a history of recurrent, severe, or unusual infections or any of the noninfectious issues discussed previously herein merits immunologic evaluation. The definition of

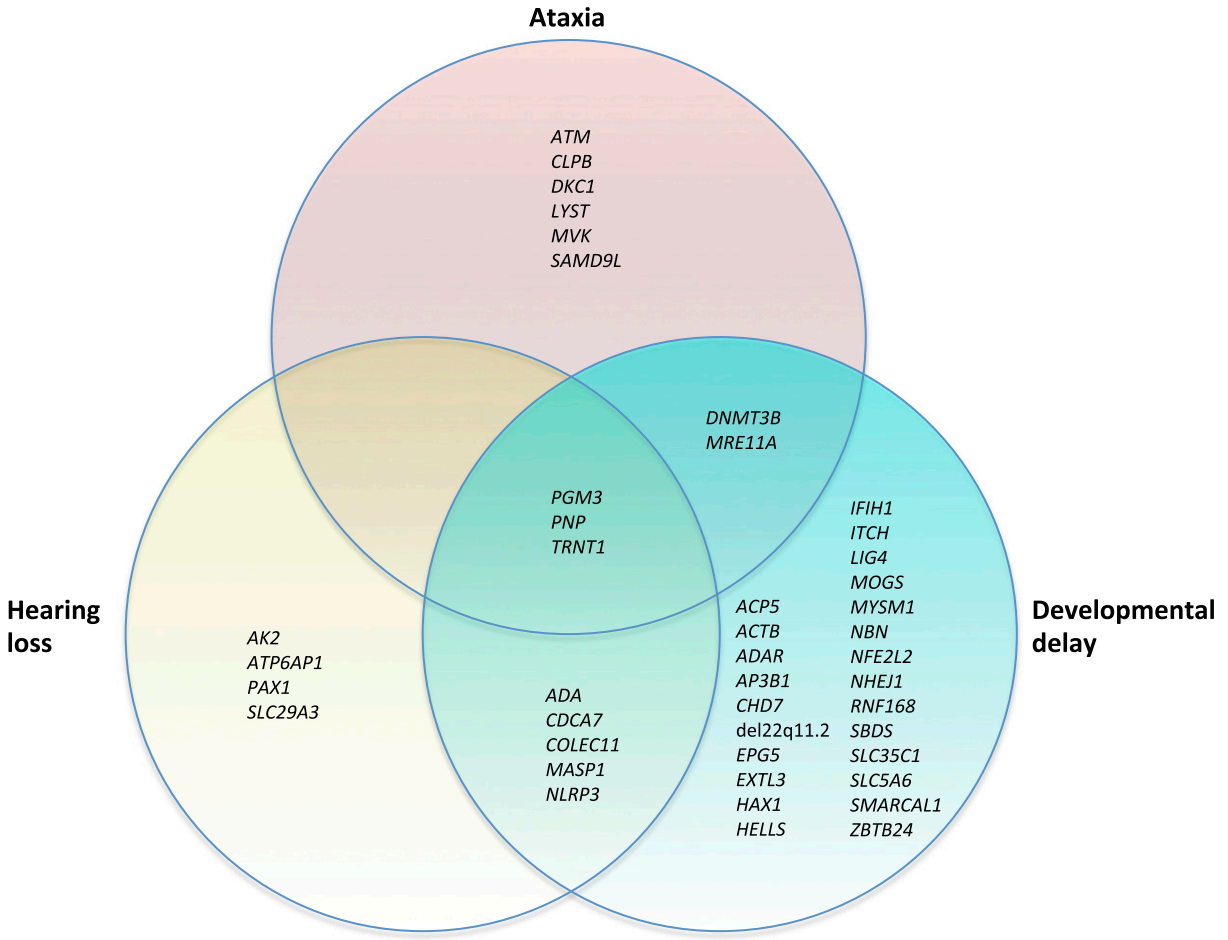


Figure 4. Neurologic manifestations of primary immunodeficiencies.

TABLE 5. **Pulmonologic Manifestations of PIDs**

CONDITION	ASSOCIATED PID GENES
Interstitial lung disease	*COPA, ITCH, STAT3, TMEM173, TNFAIP3, XIAP*
Pulmonary alveolar proteinosis	*CD40LG, CSF2RA, GATA2, SLC7A7*
Capillaritis and hemorrhage	*COPA*
Eosinophilic pneumonia	*NSMCE3*

PID=primary immunodeficiency.

recurrent remains imprecise. It may not be unusual (17% incidence rate) for a 1-year-old child to have had 3 or more episodes of otitis media, and almost half of the children will have had at least 3 occurrences of otitis media by 3 years of age. (32) One large study suggests that healthy children younger than 3 years may have 11 respiratory tract infections per year, and healthy children aged 3 to 5 years may have 8 respiratory tract infections annually. (33) Thus, clinical judgment remains necessary. As a general rule of thumb, it is the clinical practice of the authors to advise pediatricians to consider PID in their patients who distinguish themselves from the general patient population regarding the occurrence of infections. Statistically speaking, a pediatric practice of 10,000 patients will have 5 to 10 cases of PID overall. Pediatricians should, therefore, be mindful of patients who exist as outliers from an infectious standpoint so that they will be sure to capture PID cases within their practice.

Second, the family history may encourage immunologic testing. Underlying PID should be considered if family members have had recurrent or unusual infections, especially maternal uncles or other males. Other suspicious elements of the family history include consanguinity and early childhood mortality from infections or unexplained causes.

TABLE 6. **Other Noninfectious Manifestations of PIDs**

CONDITION	ASSOCIATED PID GENES
Allergies	*CARD11, CARMIL2, CTLA4, DOCK8, FOXP3, PGM3, SPINK5, WAS, WIPF1*
Skeletal dysplasia	*ACP5, ADA, ALG12, EXTL3, NBAS, PGM3, RNU4ATAC, RMRP, SMARCAL1*

PID=primary immunodeficiency.

Third, investigation for PID may be warranted in children with physical examination findings consistent with any of the noninfectious presentations mentioned. Children with failure to thrive should also raise suspicion for underlying PID. Furthermore, a child who demonstrates absent or minimal lymphatic tissue should unquestionably be assessed for an underlying PID.

Finally, infants with abnormal newborn screening tests for SCID must receive immunologic evaluation. As of the end of 2017, all but 2 states (Louisiana and Indiana) have implemented active SCID newborn screening programs. The screening test is designed to detect absent or low numbers of T-cell receptor excision circles in blood spots from Guthrie cards. (34) Thus, an abnormal newborn screening test may signify the presence of T-cell deficiency.

Laboratory Testing for PID

Several tests are recommended for initial evaluation for suspected PID. First, because defects in humoral immunity predominate, (3)(35) quantitative measurement of serum immunoglobulin levels and functional assessment of specific antibody responses provide excellent screening tests for PID. Specific antibody function should be tested by determining antibody production toward immunizations. (36) These functional activities represent the most standardized, most uniform, and best-studied humoral immune responses. As a more advanced diagnostic intervention, children older than 2 years can be additionally tested for humoral responses to the polysaccharide antigens in the 23-serotype pneumococcal polyvalent vaccine. Overall, these investigations are performed by obtaining baseline antibody titers, administering the relevant vaccine, and measuring the postimmunization titers (eg, approximately 3 weeks after immunization for tetanus toxoid; both 4 to 8 weeks and 6 months after immunization for the 23-serotype pneumococcal polyvalent vaccine). Next, a complete blood cell count with a manual differential count can be used to screen for quantitative T-cell deficiency through the absolute lymphocyte count (ALC). In a newborn, an ALC less than 2,500/μL ($<2.5 \times 10^9$/L) suggests that T cells have not developed fully and that they may even be absent in whole or in part. (37) From a PID perspective, it is essential for pediatricians to focus on and calculate the ALC in routine blood cell counts. Any abnormalities should be followed by a T-cell subset analysis performed by flow cytometry to ensure the appropriate presence and distribution of the different subpopulations. Absence of a cardiothymic silhouette on chest radiographs in an infant should also raise concern for the absence of T cells. For functional

assessment of T cells, in vivo delayed-type hypersensitivity testing by the intradermal injection of T-cell antigens such as tetanus toxoid and *Candida albicans* can be performed in the office setting, but the recommended option would consist of referral to an immunology specialist for appropriate in vitro testing. The advantage of the latter method comes from the fact that it is highly quantitative and directly comparable with reference standards. Third, a total serum hemolytic complement assay can be ordered to exclude deficiency of any of the components of the classic complement pathway. This test is highly sensitive to sample handling, and true deficiency is likely only if the total serum hemolytic complement is zero or near zero. (38) Next, a potential diagnosis of CGD should be examined using a dihydrorhodamine-1,2,3 flow cytometry–based assay. Nitroblue tetrazolium reduction is no longer preferred due to its subjectivity and lack of sensitivity. Clinicians should be aware that individuals with myeloperoxidase and glucose-6-phosphate dehydrogenase deficiencies can have abnormal dihydrorhodamine-1,2,3 test results. Children whose clinical history may suggest cyclic neutropenia should be evaluated by serial complete blood cell counts with differential counts. This protocol involves obtaining counts 2 to 3 times weekly for 6 to 8 weeks. Finally, patients for whom ataxia-telangiectasia is suspected should be screened with a serum α-fetoprotein level, which is typically elevated in affected individuals.

Children with suspected PIDs should then be referred to a clinical immunology expert for further evaluation because many different subspecialized immune tests are available that help in the further delineation of the different PIDs. Such additional laboratory testing may be warranted, and genetic testing may be considered necessary in some individuals. (18) Importantly, we are rapidly moving toward a practice environment in which broad genetic testing (such as whole exome sequencing) may actually precede formal assessment of a PID in an otherwise sick child. This approach has the potential to conserve financial resources in some cases but often leaves the geneticist and immunologist with the task of determining whether certain genetic findings represent an explanation for the clinical and immunologic presentation. A detailed discourse concerning this topic exceeds the scope of this discussion, but the reader is referred to several excellent review articles. (39)(40)(41) Nonetheless, it is essential for the pediatrician to know that several different sequencing "panels" exist to allow for follow-up assessment of abnormal SCID newborn screening tests and can capture all known SCID-associated genes with rapid turnaround. Although genetic tests are truly empowering and can be definitive, they do not replace quantitative and functional immune tests, which are still needed to understand the severity of a given gene aberration.

Management of Children with PID

Infectious complications should be minimized as much as possible, and strategies should be dictated by the susceptibilities associated with the immunologic mechanism that is impaired. These precautions are especially important because any infection in an individual with PID has the potential to become severe, and repeated chest infections in particular can increase the risk of bronchiectasis and irreversible lung damage. Trimethoprim-sulfamethoxazole prophylaxis is indicated for the prevention of *Pneumocystis* pneumonia and is also used for prophylaxis against staphylococcal and nocardial infections in CGD. Children with susceptibility to atypical mycobacterial infections should be placed on azithromycin prophylaxis, and acyclovir is recommended as a prophylactic agent in individuals who are susceptible to invasive herpes simplex virus infections. Fluconazole can be used for prophylaxis against candidal infections, although some patients with chronic mucocutaneous candidiasis will require voriconazole for complete prevention. In children with CGD, itraconazole is typically used for prophylaxis against *Aspergillus* and other fungal infections. Antifungal prophylaxis is especially important in these patients, as *Aspergillus* infection represents the most significant cause of mortality. Children who are susceptible to *Cryptosporidium parvum* infections, such as boys with X-linked hyper-IgM syndrome, should avoid water parks and tap water. Live attenuated immunizations should not be given to individuals with certain PIDs and should, therefore, be approved by an immunology specialist before administration. (36) Live attenuated immunizations should be administered to family members and household contacts, however, to provide herd protection. (42) For all children, universal precautions, such as good handwashing, should be practiced. They do not need to be "kept in a bubble" but should be excluded from contact with individuals who have infections and from environments highly enriched for pathogens, such as child care. Children with severe T-cell deficiencies require reverse isolation in clinic and hospital settings. If transfusions become necessary for these individuals, they should receive only irradiated, cytomegalovirus-negative blood products. In all children with PIDs, a low index of suspicion should be entertained for infections. Antimicrobial drug therapy should be given promptly and withdrawn cautiously. It is also important to note that many of these practices become unnecessary in

patients who have achieved full immune reconstitution through definitive curative measures, such as hematopoietic stem cell transplant or gene therapy.

Finally, more advanced treatment options should be pursued with input from an expert in PIDs. For example, IgG replacement is fully indicated as a therapy for PIDs that contain humoral deficiency as a component and should be used to treat such patients with PID accordingly. (43) Certainly, a wide array of IgG replacement options exists, and best practice continues to evolve. (44) Furthermore, as knowledge increases regarding the defective mechanisms responsible for impaired immunity for various PIDs, novel targeted biological therapies are being developed and tested to more specifically restore appropriate immune function in these individuals. (45)(46) Ultimately, the greatest opportunity for definitive treatment for most children with PIDs will come through continued improvements in hematopoietic stem cell transplant and increasing advances in gene therapy, as directed by an immunology specialist.

SECONDARY IMMUNODEFICIENCIES

Secondary causes of immunodeficiency should always be excluded in children with suspected PIDs. A brief review of these etiologies follows.

Iatrogenic causes of immunodeficiency must be considered. Medications stand as well-established causes of IgA deficiency and include antiepileptic drugs, such as phenytoin, carbamazepine, valproic acid, and zonisamide. (47) IgA deficiency has also been linked to use of nonsteroidal anti-inflammatory drugs. (47) Other medications associated with hypogammaglobulinemia include anti-inflammatory compounds (eg, sulfasalazine, gold, penicillamine, and hydroxychloroquine). (48) Many medications given for chemotherapy in the transplant setting or for treatment of malignancies, such as cyclosporine, tacrolimus, mycophenolate mofetil, cyclophosphamide, azathioprine, and 6-mercaptopurine, can cause hypogammaglobulinemia and secondary T-cell deficiencies. Corticosteroids also suppress T-cell function and impair wound healing, and they have been proposed to induce hypogammaglobulinemia if administered for extended periods. (48) Targeted biological modifiers are being implemented in a variety of disease conditions, such as autoimmune or inflammatory diseases and solid organ transplant, and they have been demonstrated to cause secondary immunodeficiency. (46)(49) The primary mechanism consists of intentional disruption of the immunologic host defense processes that are causing the undesirable clinical condition. For example, individuals who are receiving anti–tumor necrosis factor α therapy for inflammatory bowel disease are well-known to have increased risk for *Mycobacterium tuberculosis* infection or reactivation. Several newer biologic therapies (*eg*, rituximab and anti-CD19 chimeric antigen receptor T cells) are designed to cause depletion of B cells and result in hypogammaglobulinemia. Finally, surgical injury to the thoracic duct can cause hypogammaglobulinemia and quantitative T-cell deficiency through loss of lymphatic contents into the pleural cavity.

Other mechanisms of immunoglobulin and lymphocyte losses must be excluded as well. Additional explanations for pulmonary losses include chylothorax or exudative pleural effusions from obstruction of lymphatic flow or perturbed intrathoracic pressure. Gastrointestinal losses can also represent a significant cause of secondary immunodeficiency. Hypogammaglobulinemia, particularly loss of IgG, and lymphopenia can be observed in children with intestinal lymphangiectasia. Other sources of gastrointestinal losses include inflammatory bowel disease and chronic diarrhea. Last, nephrotic syndrome can even lead to IgG deficiency in some patients through urinary losses.

Nutritional status cannot be underestimated as a secondary cause of immunodeficiency, and it is said to represent the most common cause of an immune deficiency. (50)(51) Severe malnutrition results in decreased production of secretory IgA by mucosal tissues and lower numbers of B cells. Thymic involution occurs, total T and $CD4^+$ T-cell counts decrease, and T-cell proliferation to mitogens and antigens becomes diminished. The absence of specific nutrients can affect immunity in a variety of manners. For example, lack of protein results in overall leukopenia and diminished innate immune function. (52) Zinc deficiency, on the other hand, results in impaired neutrophil chemotaxis and phagocytosis, natural killer cell cytotoxicity, and T-cell differentiation. (53) Vitamin E deficiency has been reported to cause decreased T-cell function, and vitamin B_6 deficiency is associated with lymphopenia, decreased antibody production, and lower T-cell proliferative responses to mitogens. (54) Furthermore, vitamin C deficiency is known to result in susceptibility to infections, especially pneumonia, and poor wound healing through impaired neutrophil chemotaxis, phagocytosis, and killing activity. (55) On the opposite end of the spectrum, obesity can impair neutrophil activity, lymphocyte proliferation, and T-cell development. (56) Thus, nutritional factors must be assessed.

Physiologic and psychological stress can also cause secondary immunodeficiency. (57) For example, critically ill postinjury patients have been shown to have impaired neutrophil phagocytosis and killing of *S aureus*. (58) As a second example, brain injury induces interleukin-10–mediated suppression of immune function. (59) In addition, psychosocial stressors can certainly affect children, whether at home, at school, or in other settings. For instance, children with depression can have decreased neutrophil phagocytosis and bactericidal activity toward *S aureus*. (60) On the whole, few studies have examined the effect of psychological stressors on immune function in children, but lessons may be learned from stress in adults, which is associated with reduced secondary antibody responses and lymphocyte proliferative responses to mitogens among other immunologic changes. (61)(62)

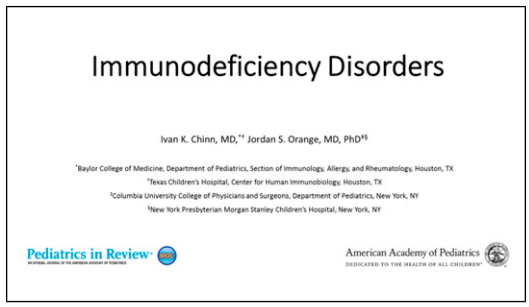
Human immunodeficiency virus (HIV) infection remains the most well-studied cause of secondary immunodeficiency; a comprehensive discussion remains beyond the scope of this review. HIV infection should be excluded by antibody- and antigen-based assays combined with nucleic acid testing. (63) For neonates, only virologic testing should be performed due to transmission of maternal antibodies. These nucleic acid–based tests should be performed at ages 14 to 21 days, 1 to 2 months, and 4 to 6 months. (64)

Other factors should be investigated as potential secondary causes of immunodeficiency. Anatomical issues, such as eustachian tube dysfunction and congenital fistulas, can lead to recurrent infections. Atopy can produce adenoidal hypertrophy that results in recurrent otitis media or sinusitis. It can also contribute to asthma, which may be misdiagnosed as recurrent pneumonia or bronchitis. Furthermore, allergic sensitization can exacerbate eczema, which can predispose toward recurrent cutaneous infections. In terms of oncologic etiologies, multiple myeloma and chronic lymphocytic leukemia are known to produce secondary immunodeficiency, but these malignancies do not commonly occur in children. (65) No large studies have been conducted to examine the prevalence of secondary immunodeficiency in pediatric malignancies, however. Other disease conditions, such as cystic fibrosis and diabetes mellitus, (66) are known to favor the appearance of recurrent infections. SLE has been associated with IgA deficiency, but it remains uncertain whether the correlation is causal. (67)(68) Certainly, some effect on immune function is likely, as 1 of the 11 criteria used for diagnosis includes leukopenia or lymphopenia. Infections themselves can suppress immunity. A well-established example is provided by measles infection, which can produce profound impairment of B- and T-cell function. (69) Finally, preterm infants are born with an immunocompromised state. (70) Transfer of maternal antibodies begins during the second trimester but accelerates during the final trimester. Mature T cells can be detected at 15 to 16 weeks of gestation, but polyclonal repertoire diversity is not achieved until 22 to 26 weeks of gestation, and thymic output remains low, resulting in low T-cell receptor excision circle levels and abnormal newborn screening tests for SCID. (71)(72)

CONCLUSIONS

Clinicians must maintain a high index of suspicion for immunodeficiency disorders in pediatric patients. Decades of ongoing exploration and study affirm the notion that PIDs are neither rare nor necessarily intimidating to diagnose and manage. Instead, timely recognition of these conditions followed by appropriate testing and referral to an immunology specialist remains indispensable for realizing essential strategies to provide optimal health and well-being for these children. As such, early symptoms or cues present a critical window of opportunity during which a diagnosis can be established while still permitting transformative or even curative treatments to promote longevity and quality of life.

***To view teaching slides that accompany this article, visit* http://pedsinreview.aappublications.org/content/40/5/229.supplemental.**



Summary

- Based on growing research evidence as well as consensus, primary immunodeficiencies (PIDs) are not rare conditions. More than 300 different PIDs exist, and the prevalence of PID is approximately 1 in every 1,200 to 2,000 individuals. (1)(2)(3) Because most PIDs have well-defined genetic etiologies, in the evaluation for PID, clinicians should solicit information about consanguinity or about family members with immune deficiency, recurrent or severe infections, or early mortality.
- Based on strong research evidence as well as consensus, severe combined immunodeficiency disease (SCID) is a pediatric emergency due to profound absence of humoral and cellular immunity secondary to lack of T cells. (6)(7) The condition may be recognized by abnormal newborn screening test results, an absolute lymphocyte count less than 2,500/μL (2.5×10^9/L) in a term neonate, opportunistic infections, absence of cardiothymic silhouette in an infant, failure to thrive, and paucity of lymphatic tissues. In fact, all pediatric patients who have unexplained failure to thrive and lack of lymphoid tissue should be assessed for PID. Any concern for SCID warrants prompt evaluation by an immunology specialist.
- Based on consensus as well as some research evidence, receipt of an abnormal newborn screening test result for SCID should compel the pediatrician to obtain immediate consultation with an immunology specialist. A complete blood cell count with a manual differential count should be obtained expeditiously to assess for absolute lymphopenia. (36)
- Based on collective research evidence as well as consensus, although healthy children may have more than 3 episodes of otitis media and up to 11 upper respiratory tract infections each year, (31)(32) children with uncharacteristically recurrent, severe, or unusual infections should be tested for PIDs. Children with recurrent sinopulmonary tract infections, especially after 3 to 4 months of age, should be evaluated for humoral immune deficiencies and other PIDs. (5) Children with invasive infections and poor wound healing should be tested for defects in phagocytic number or function. Chronic granulomatous disease should be suspected in a child with infection due to an unusual bacterial or fungal organism. (8)(10) Natural killer cell deficiency should be considered in a child with recurrent, severe, or unusual herpesviral infections. (11)(12) Children with atypical mycobacterial infections and chronic mucocutaneous candidiasis should be assessed for PIDs. (13)(14) Children with susceptibility to neisserial pathogens should be evaluated for primary complement deficiencies. (17)
- Based primarily on consensus due to lack of large clinical studies, children with PIDs can present with noninfectious issues. Children with early- or very early–onset enteropathy or inflammatory bowel disease should be evaluated for underlying PIDs. (19) PIDs should be considered in children with severe eczema, neutrophilic pustular dermatosis, ectodermal dysplasia, cutaneous granulomas, abnormal skin or hair pigmentation, and cold-induced urticaria. (20)(21) PIDs can be associated with early-onset autoimmune disease. (22)(23)(24)(25)(26) Children with early-onset endocrinopathies should be evaluated for underlying PIDs. PIDs can also present in children as lymphoproliferative disease and hemophagocytic lymphohistiocytosis. (28) Several neurologic signs, including ataxia, hearing loss, and developmental delay, are associated with PIDs. (29)(30) Children with PIDs are known to present with interstitial lung disease, pulmonary alveolar proteinosis, pulmonary capillaritis, or eosinophilic pneumonia. Allergies and skeletal dysplasia can be associated with PIDs.
- Based on consensus as well as established research evidence, although children with suspected PID should be referred to an immunology specialist for assistance with diagnostic evaluation, test results interpretation, and management recommendations, there are widely available testing methods for evaluating for PIDs before referral. Because most PIDs affect humoral immunity, children with suspected PIDs should be screened by measurement of serum immunoglobulin levels and specific antibody responses to immunizations. (3)(34)(35) Additional tests that should be considered include an absolute lymphocyte count to evaluate for quantitative T-cell deficiency, delayed-type hypersensitivity skin testing to examine T-cell function, a total serum hemolytic complement assay to investigate for primary complement pathway deficiencies, and a dihydrorhodamine-1,2,3 assay to assess for chronic granulomatous disease.
- Based on consensus as well as some research evidence, in children with PIDs, infections should be minimized using appropriate antimicrobial prophylaxes, social and environmental preventive measures, and other universal precautions.
- Based on strong research evidence as well as consensus, IgG replacement stands as an effective and potentially lifesaving treatment for children with severe or functional humoral immune deficiency. (42)(43)
- Based on some research evidence as well as consensus, secondary causes of immunodeficiency must be excluded in children with suspected PIDs. Various medications, especially antiepileptic, anti-inflammatory, chemotherapeutic, and immune modulatory compounds, are known to cause secondary immunodeficiencies. (45)(46)(47)(48) Physiologic losses of immunoglobulins and lymphocytes can result in secondary immunodeficiency. Nutritional deficits and excess can produce secondary immunodeficiency, as can physiologic and psychosocial stress. (49)(50)(51)(52)(53)(54)(55)(56)(57)(58)(59)(60)(61) Human immunodeficiency virus infection must be excluded in children with suspected immunodeficiency. (62)(63) Other common secondary causes of immunodeficiency that must be considered include anatomical mechanisms, atopy, other underlying disease conditions, infection-induced immune suppression, and prematurity. (64)(65)(66)(67)(68)(69)(70)(71)

References for this article are at http://pedsinreview.aappublications.org/content/40/5/229.

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1. A 5-year-old girl, new to your practice, is brought to the clinic by her parents with concerns for attention-deficit/hyperactivity disorder and autism because of her cognitive and behavioral problems. Her medical history is significant for tetralogy of Fallot, which was repaired at 5 months of age, frequent upper respiratory tract infections, and recurrent tinea capitis. Which of the following is the most likely diagnosis to consider in this patient?
    A. Aicardi-Goutières syndrome.
    B. Chédiak-Higashi syndrome.
    C. Chronic granulomatous disease.
    D. DiGeorge syndrome.
    E. Wiskott-Aldrich syndrome.
2. A 6-year-old girl in your practice has a history of severe eczema, recurrent staphylococcal abscesses, mild facial dysmorphism, and scoliosis. Her older sister has similar symptoms and her mother has a history of recurrent skin and lung abscesses. Which of the following laboratory tests is the most appropriate initial test that is likely to be useful in making a diagnosis in this patient?
    A. Total serum hemolytic complement level.
    B. Dihydrorhodamine-1,2,3 flow cytometry.
    C. Platelet count.
    D. Quantitative immunoglobulins.
    E. T-cell flow cytometry.
3. A 1-month-old infant, followed in your practice, is found to have an absent thymic shadow when a chest radiograph was obtained during an episode of bronchiolitis. A complete blood cell count demonstrates marked lymphopenia. Which of the following is the most appropriate next step in the care of this infant?
    A. Initiate antibiotic prophylaxis with azithromycin.
    B. Measure quantitative immunoglobulins.
    C. Obtain a complete blood cell count with a manual differential count twice weekly for 6 to 8 weeks.
    D. Refer to an immunology specialist.
    E. Test for human immunodeficiency virus infection using a nucleic acid–based test.
4. A 30-month-old boy was hospitalized for operative drainage of bilateral cervical adenitis due to *Staphylococcus aureus* infection. His medical history includes a previous hospitalization for pneumonia with blood culture positive for *Klebsiella pneumoniae*, as well as recurrent fevers and pyoderma. Dihydrorhodamine-1,2,3 assay results are abnormal. Which of the following is the most likely diagnosis in this patient?
    A. Ataxia-telangiectasia.
    B. Chronic granulomatous disease.
    C. Common variable immunodeficiency.
    D. Cyclic neutropenia.
    E. Leukocyte adhesion deficiency.
5. Newborn screening results for an infant in your practice have just returned positive for severe combined immunodeficiency (SCID). Which of the following is the most appropriate next step in the management of this patient?
    A. Measure quantitative immunoglobulin levels.
    B. Order a gene sequencing panel for SCID.
    C. Reassure the parents that this is likely a false-positive result.
    D. Repeat the newborn screen.
    E. Seek immediate specialty consultation.

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Immunodeficiency Disorders

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