

# Primary Immunodeficiency Masquerading as Allergic Disease



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## KEYWORDS

- Primary immune deficiency • Corticosteroids • Eczema • Elevated IgE
- Allergic disease

## KEY POINTS

- Primary immune deficiencies (PIDs) are uncommon diseases, including several with overlapping clinical presentations to common allergic and autoimmune diseases.
- Early recognition and diagnosis of PIDs is critical.
- Immune suppression should be initiated judiciously because it can increase the susceptibility to life-threatening diseases in PID patients.

## INTRODUCTION

Primary immune deficiencies (PIDs) are an uncommon heterogeneous group of diseases that result from fundamental defects in the proteins and cells that enable specific immune responses. Most are inherited and often appear in family members. Remarkably, many of these diseases do not demonstrate predictable clear-cut clinical patterns. For many, the hallmark is an increased susceptibility to infection; and different pathogens associate with different defects of the immune system. The true incidence and prevalence of these primary immunodeficiencies are unknown, but are estimated to be 1:10,000 to 1:2000 from registries in more than 40 countries.<sup>1</sup> This is likely an underestimation because many cases remain undiagnosed; a random telephone survey in the United States estimated the prevalence of all PIDs at 1:2000 to 1:800.<sup>2</sup> Early diagnosis of a PID has a significant bearing on outcome. For example, newborn screening for severe combined immune deficiency (SCID) has resulted in important early diagnoses and when treated with hematopoietic stem cell transplantation (HSCT) before 3.5 months of age, a 94% success rate can be achieved compared with older individuals with infections at the time of transplant (50%).<sup>3</sup>

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What is increasingly being recognized is that common allergic symptoms can also be manifestations of an underlying and severe immune deficiency (**Fig. 1**). The immune system relies on a complex balance of activation, to protect against invading pathogens, and control, to discriminate between self, nonself, and foreign matter. Hypersensitivity (allergic) reactions (eczema, allergic rhinitis, asthma, and food allergies) are exaggerated immune responses against specific allergens. Classic testing used to investigate allergic diseases often reveals increased immunoglobulin (Ig)E, peripheral blood eosinophilia, and immediate skin responses after percutaneous or intradermal injection. It is now clear that some of these PIDs do not manifest with a predominant susceptibility to infection, but rather present with what seems to be more common allergic symptoms or autoimmunity.<sup>4</sup> Recognition of these immunodeficiencies is important because their treatments are profoundly different than the treatments for an allergic condition, the latter often involving use of immunosuppressive therapies. In PID patients, further suppression of the immune system increases susceptibility to a life-threatening event, namely, infection. If the classic allergic triad includes increased IgE, eosinophilia, and eczema, then under this umbrella are a number of genetically defined PIDs that masquerade as allergy and warrant different therapeutic approaches (**Table 1**).

### ALL THAT ITCHES IS NOT ALWAYS ECZEMA

Eczema is a complex, chronic, relapsing inflammatory skin disorder with a lifetime prevalence in the United States of 17%.<sup>5</sup> Interestingly, 80% have an elevated serum IgE.<sup>6</sup> It is the earliest part of the allergic march toward allergic rhinitis and asthma, with 66% of patients progressing to develop asthma plus at least 1 allergy by 3 years of age.<sup>7</sup>

#### *Pathophysiology*

Eczema and atopic dermatitis present early in infancy, usually between 1 and 6 months of age. Resolution occurs in 50% by adolescence, but factors that suggest a poorer prognosis include family medical history of eczema, early infantile disease, gender (female), coexistent allergic rhinitis, or asthma.<sup>8</sup> Although the exact mechanism remains unclear, breaks in the skin barrier lead to sensitization to allergens, increased IgE levels, and increased numbers of eosinophils.

### PRIMARY IMMUNE DEFICIENCY PRESENTING WITH NEWBORN AND INFANT ECZEMA

Although a common condition, eczema in a newborn warrants a number of diagnostic considerations and concerns. Severe whole body dermatitis appearing as an

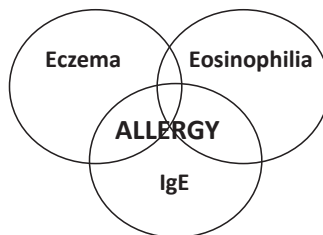


**Fig. 1.** The allergic triad. Allergic diseases share common factors with primary immunodeficiencies including skin rashes such as eczema, increased immunoglobulin (Ig)E, and eosinophilia.

**Table 1**  
Phenotypic expression of eczema, eosinophilia, and increased IgE in primary immunodeficiency

| Eczema         | Eosinophilia | Increased IgE |
|----------------|--------------|---------------|
| IPEX           | IPEX         | IPEX          |
| Omenn          | Omenn        | Omenn         |
| AD-HIES        | AD-HIES      | AD-HIES       |
| AR-HIES        | AR-HIES      | AR-HIES       |
| Wiskott-Adrich | —            | —             |

Various primary immunodeficiencies have a predominance in manifestation of their disease.

**Abbreviations:** AD-HIES, autosomal-dominant hyper-IgE syndrome; AR-HIES, autosomal recessive hyper-IgE syndrome; Ig, immunoglobulin; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome.

eczematous rash and loose stool/diarrhea may be mistaken as an atopic baby with food allergy. Clinicians should consider PIDs especially if standard interventions with topical steroids and changing formulas are helpful only transiently. PIDs may mimic allergic atopic patients.<sup>4</sup>

### **Human Immunodeficiency Virus**

Infants with human immunodeficiency virus (HIV) infection (a secondary immunodeficiency) can present with eczematous rash, high IgE, and failure to thrive. It is one of the more common immunodeficiencies and should always be excluded when considering a PID. Virologic testing with HIV DNA polymerase or HIV RNA assays should be used.

### **Omenn Syndrome**

Omenn syndrome is an inflammatory condition characterized by erythroderma, desquamatus alopecia, chronic diarrhea, failure to thrive, lymphedema, and hepatomegaly.<sup>9</sup> It was originally described in 1965 with reticuloendotheliosis and eosinophilia.<sup>10</sup> The prevalence is estimated at less than 1/1,000,000.<sup>11</sup> It is linked to SCID and presents in the first year of life, but the signs and symptoms evolve over time. These patients are highly susceptible to the infections that are typically seen in SCID patients.

### **Pathogenesis**

There are no specific genetic defects for Omenn syndrome. It is an inflammatory phenotype of SCID that has been linked to mutations in the recombination-activating gene 1 (RAG1) or RAG2, RNA component of mitochondrial RNA processing endoribonuclease, adenosine deaminase, interleukin (IL)-2R, IL-7R, artemis-nuclease-DCLRE1C DNA ligase 4, and 22q11 microdeletion. It usually presents in an autosomal-recessive pattern. This is a “leaky” T/B-SCID phenotype where some T or B cells are present and suggestive of mutations that lead to impairment of the V(D)J DNA recombination involved in generating immunoglobulins as well as T-cell receptors.

### **Diagnosis**

Omenn syndrome is characterized by clinical inflammation with abnormal T-cell populations. Lymphocyte phenotyping by flow cytometry show T-cell lymphopenia or oligoclonality that have impaired function. Typically, B cells are absent with loss of IgG, IgA, IgM, but increased serum IgE. Peripheral blood eosinophilia is also present. Skin biopsy of lesions show acanthosis and parakeratosis.

### ***Differential diagnosis***

In addition to Omenn syndrome, infants with severe eczematous dermatitis with diarrhea may not just be a severely atopic infant with food allergy, but consideration of other PIDs include an SCID patient with maternal T-cell engraftment syndrome causing graft versus host disease, infantile ichthyosis, histiocytosis, and hyper-IgE syndrome.

### ***Management***

Given the rarity of PIDs, unlike HIV, therapies have not been studied in large-scale clinical trials, but only in small series or case reports. Immunosuppressive treatment has been used in Omenn syndrome to control inflammation. Suppression can result in almost complete resolution of the dermatitis, alopecia, hepatosplenomegaly, and lymphadenopathy with significant weight gain.<sup>12</sup> Care should be taken to treat underlying infections and screening for opportunistic infections should be initiated before immune suppression, given the underlying SCID phenotype. To date, curative treatment and ultimate resolution requires HSCT.<sup>13</sup>

### ***X-linked Immunodysregulation, Polyendocrinopathy, and Enteropathy***

Infants with immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) usually present with severe diarrhea owing to enteropathy, endocrinopathy usually manifesting as type 1 diabetes mellitus, and dermatitis (eczema, erythroderma). Other features may include hypothyroidism, autoimmune hemolytic anemia, thrombocytopenia, lymphadenopathy, hepatitis, and nephritis. IPEX was originally described in 1982<sup>14</sup> and the prevalence is estimated at less than 1 in 1,000,000<sup>15</sup> with only around 200 cases reported to date. Patients present in the first year of life and severity varies.

### ***Pathogenesis***

IPEX is an X-linked recessive disease caused by a mutation in the FoxP3 gene on chromosome Xp11. This transcription factor plays an important role in the development and function of T regulatory cells that are actively involved in suppressing the immune system and in self-tolerance.<sup>16</sup> These T regulatory cells (CD4<sup>+</sup>25<sup>+</sup>) control T- and B-cell inflammatory reactions. FoxP3 binds to the FOX-binding site within the IL-2 promoter and suppresses its activity.

### ***Diagnosis***

IPEX patients have elevated IgE, IgA, and peripheral blood eosinophilia. The diagnosis is often made after endoscopy. Enteric biopsy may reveal villous atrophy reminiscent of severe gastrointestinal graft versus host disease or autoimmune enteropathy (with the presence of antienterocyte, harmonin, and villin autoantibodies). Evaluation for IPEX should follow the diagnosis of infant-onset insulin-dependent diabetes mellitus. It is linked to type 1 diabetes mellitus (antibodies against insulin, pancreatic islet cells, or antigitamate decarboxylase), thyroiditis (antithyroglobulin and antimicrosome peroxidase antibodies), and cytopenia (antiplatelet and antineutrophil antibodies, positive Coombs test). Lymphocyte subset phenotyping with flow cytometry shows loss of CD4<sup>+</sup>25<sup>+</sup> T regulatory cells. Molecular diagnosis with identification of mutations in FoxP3 confirms IPEX and it can identify aberrant sequences that result in termination/frameshift/missense mutations. Location and identification of the mutation can help to stratify for progression and severity of disease.<sup>17</sup>

### ***Differential diagnosis***

The triad of endocrine dysfunction, enteropathy, and inflammatory eczema in infant males is suggestive of IPEX, although other diseases should be considered, including IPEX-like syndrome in CD25 mutations that affect both genders; STAT5b mutation;

ITCH syndrome, the Nedd4 family of HECT domain E3 ubiquitin ligase mutation; Schmidt syndrome/autoimmune polyendocrinopathy syndrome type 1; autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy; Wiskott–Aldrich; STAT1 (gain of function); X-linked autoimmune enteropathy; and X-linked thrombocytopenia.

### **Management**

Supportive care (including parenteral nutrition, blood transfusions, and controlling diabetes) are the mainstays of treatment. High-dose corticosteroids, cyclosporine, tacrolimus, methotrexate, infliximab, and rituximab have been used. Sirolimus has been effective.<sup>18</sup> Allogeneic HSCT resulted in a rapid and sustained decrease in symptoms of enteropathy, eczema, and diabetes, which was accompanied by a decrease in the concentration of autoantibodies directed against pancreatic proteins.<sup>19,20</sup> HSCT for IPEX is still evolving and consultation with experts in bone marrow transplantation is important because reduced-intensity conditioning regimens using alemtuzumab, fludarabine, and melphalan may be beneficial.<sup>21</sup> Activation of the immune system makes symptoms, including blood glucose levels, more difficult to control. Extensive infectious and virology-based studies should be investigated and early treatment initiated.

### **Wiskott–Aldrich Syndrome**

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Infant males with severe diarrhea, eczema, and thrombocytopenia should be evaluated for Wiskott–Aldrich syndrome. Because of severe thrombocytopenia (which typically causes bloody diarrhea), most cases present with hemorrhagic manifestations of this syndrome yet eczematous skin lesions are readily visible. These males are prone to recurrent infections, with a component of autoimmunity in approximately 40% of cases. It was originally described in 1954,<sup>22</sup> and the prevalence is estimated at around 4 in 1,000,000.<sup>23</sup>

### **Pathogenesis**

Wiskott–Aldrich syndrome is an X-linked recessive disease owing to hemizygous mutations in the Wiskott–Aldrich syndrome gene (Xp11.4-p11.21), coding for the Wiskott–Aldrich syndrome protein (WASp), which is exclusively expressed in hematopoietic cells and plays a critical role in the organization of the actin cytoskeleton. WASp is involved in T-cell actin reorganization,<sup>24</sup> coupling surface Ig and signal transduction for B-cell activation,<sup>25</sup> as well as natural killer (NK) cell cytotoxicity. All immune cells, B, NK, and T cells are affected, resulting in a combined phenotype.

### **Diagnosis**

Wiskott–Aldrich syndrome has a typical triad of thrombocytopenia, eczema, and recurrent infections. These patients have elevated IgE, IgA, and eosinophilia. They have thrombocytopenia with reduced platelet size and a normal number of megakaryocytes, as well as impaired antibody production (mainly antipolysaccharide antibodies). The molecular diagnosis with loss of WASp confirms Wiskott–Aldrich syndrome. Genetic diagnosis to identify aberrant sequences that result in termination/frameshift/missense mutations may help to predict disease course and prenatal diagnosis should be considered in familial cases.

### **Differential diagnosis**

Males with recurrent infections, eczema, and thrombocytopenia suggests Wiskott–Aldrich syndrome, but other syndromes to consider include Wiskott–Aldrich syndrome-2 (WAS2) caused by mutations in the WAS/WASL-interacting protein family member 1 (WIPF1) gene coding for a protein that stabilizes and prevents the degradation of WASp, acute or chronic idiopathic thrombocytopenia, and thrombocytopenia-absent radius syndrome.

**Management**

Patients with Wiskott–Aldrich syndrome may require intensive support with parenteral nutrition, blood transfusions, platelet transfusions, and intravenous immunoglobulin. Agonists of the thrombopoietin receptors (such as romiplostim and eltrombopag) have been used with some success. The only curative treatment to date is HSCT. The goal is to control the autoimmune manifestations and bleeding disorder, without further suppressing the immune system. Wiskott–Aldrich syndrome patients are prone to tumors (mainly B-cell lymphomas). Interesting *in vivo* reversions have been reported.<sup>26,27</sup> Gene therapy is being trialed in cases where there is no adequate HSCT match, but remains experimental.<sup>28,29</sup>

**PIDS PRESENTING WITH EOSINOPHILIA, INCREASED IMMUNOGLOBULIN E, AND ECZEMA: IT MAY NOT JUST BE ATOPY**

***Autosomal-Dominant Hyper-immunoglobulin E Syndrome–Job Syndrome***

Autosomal-dominant hyper-IgE syndrome (AD-HIES), also known as Job syndrome, characteristically features chronic eczema, recurrent staphylococcal skin infections, increased serum IgE, and eosinophilia. Patients usually have a distinctive coarse facial appearance, abnormal dentition with retained primary teeth, hyperextensibility of the joints, and bone fractures.<sup>30</sup> They are prone to infections: recurrent “cold” skin abscesses (lacking the classical feature of red, warm, tender abscesses filled with pus), pneumonia with pneumatocele formation, and mucocutaneous candidiasis (Table 2). Interestingly, many feel fine even during severe infections. HIES was

| Table 2<br>AD-HIES and AR-HIES                         |         |         |      |
|--------------------------------------------------------|---------|---------|------|
| Gene Association                                       | AD-HIES | AR-HIES |      |
|                                                        | STAT3   | DOCK8   | TYK2 |
| Mostly de novo mutations                               | X       | —       | —    |
| Increased IgE                                          | X       | X       | X    |
| Eczema                                                 | X       | X       | X    |
| Eosinophilia                                           | X       | X       | X    |
| Coarse facies                                          | X       | —       | —    |
| Skeletal abnormalities                                 | X       | —       | —    |
| Retained primary teeth                                 | X       | —       | —    |
| Hyperextensible joints                                 | X       | —       | —    |
| Pulmonary pneumatocele                                 | X       | —       | —    |
| Viral skin infections                                  | —       | X       | X    |
| Asthma                                                 | —       | X       | —    |
| Food allergies                                         | —       | X       | —    |
| Decreased IgM                                          | —       | X       | —    |
| Mycobacterium susceptibility                           | —       | —       | X    |
| Difficulty handling herpes simplex virus and Molluscum | —       | X       | X    |
| CNS manifestations                                     | —       | X       | X    |
| Cerebral vascular malformations                        | —       | X       | X    |

The 2 predominant inherited forms of hyper-IgE syndrome have overlapping similarities, as well as distinct differences that can suggest the underlying genetic defect

*Abbreviations:* AD-HIES, autosomal-dominant hyper-IgE syndrome; AR-HIES, autosomal-recessive hyper-IgE syndrome; CNS, neurologic; IG, immunoglobulin.

originally described in 1966.<sup>31</sup> Serum IgE levels are often greater than 2000 IU/mL, eosinophilia often greater than 700 cells/mL, but patients usually lack any symptomatic allergic disease such as allergic rhinitis, food allergy, or anaphylaxis.

The overlapping clinical features with atopic patients led to clinical scoring criteria to assess the probability of AD-HIES. In 1999, the National Institutes of Health HIES scoring system was developed where a score of greater than 15 indicated that AD-HIES was likely owing to STAT3 deficiency.<sup>32</sup> This was further refined based on a total IgE concentration greater than 1000 IU/mL and a weighted score of clinical features so that a score greater than 30 predicts a STAT3 mutation.<sup>33</sup> Approximately 60% to 70% of cases are the result of a dominant-negative mutation in the signal transducer and activator of transcription 3 (STAT3) gene.<sup>33</sup> The etiology in the remaining 30% is unknown, and the prevalence is estimated between 1 and 9 in 100,000.<sup>34</sup>

### **Pathogenesis**

A dominant-negative heterozygous mutation in STAT3 leads to AD-HIES. STAT3 is located at 17q21.31 and is critical in the signal transduction of a broad range of cytokines that act as transcription activators. Phosphorylation of tyrosine 705 leads to activation and the formation of homodimers or heterodimers, which then translocate to the cell nucleus. They respond to cytokines and growth factors including: interferons, epidermal growth factor, IL-5, IL-6, hepatocyte growth factor, leukemia inhibitory factor, bone morphogenetic protein 2, IL-10, and leptin. The loss of function results in the failure of cells to respond appropriately to normal signaling.

There is a decrease in central memory (CD4- and CD8-positive T cells expressing CD27 and CD45RO) not due to apoptosis or cell turnover and stimulation of naive T cells with IL-7 or IL-15 failed to restore memory cell generation.<sup>35</sup> Defects in STAT3 decreases signaling through the T helper 1 pathway and skews toward T helper 2 cytokine production. Most cases are caused by de novo mutations.

### **Diagnosis**

AD-HIES as a result of STAT3 dominant-negative mutations lead to eosinophilia and increased serum IgE. Often, the baseline increased total white blood cell count does not increase with acute infection. Neutropenia is rare, but has been reported, as have normal Ig levels. Numbers of T helper 17 cells assessed by flow cytometry or STAT3 phosphorylation are low. The gold standard is molecular diagnosis with sequencing of STAT3. Prenatal diagnosis is possible in familial STAT3 mutations.

### **Differential diagnosis**

The HIES scoring system helps stratify the likelihood of a STAT3 mutation.<sup>33</sup> Other diseases should also be considered, including severe atopic dermatitis, cystic fibrosis, HIV, chronic granulomatous disease, and autosomal-recessive HIES (AR-HIES).

### **Management**

Prevention and management of infections with long-term systemic antibiotics and antifungals is important. Lung abscesses may require operative intervention and aggressive management of possible complications. Although there is significant mortality, life expectancy can reach 50 years. Because some patients fail to sustain protective vaccination titers, Ig replacement should be initiated. HSCT is still under investigation, but has been used in severe disease.

### **Autosomal-Recessive Hyper-immunoglobulin E Syndrome**

AR-HIES is also characterized by chronic eczema, recurrent staphylococcal skin infections, increased serum IgE, and peripheral blood eosinophilia. Clinically distinct

from AD-HIES, these patients rarely have skeletal/dental abnormalities or coarse facial features. They are susceptible to severe viral infections (ie, herpes simplex virus, varicella zoster virus, and molluscum), and central nervous system manifestations (facial paralysis, hemiplegia, ischemic infarction, and subarachnoid hemorrhage), autoimmune diseases, and vascular disorders (aneurysms) are variably associated. Poor growth and failure to thrive is common. Unlike AD-HIES, 50% to 70% of patients develop severe allergies, including eczema, anaphylaxis to food, and environmental allergies, and 30% have asthma.<sup>36</sup> Pulmonary disease is usually asthma-related as compared with AD-HIES, where resulting pneumatocele and lung damage are the result of prior infections.

AR-HIES was originally described in 2004.<sup>37</sup> Most cases are caused by a defect in dedicator of the cytokinesis 8 (DOCK8) gene, and clinical features vary. In 2006, a defect in the signaling protein tyrosine kinase 2 (TYK2) was also identified as being inherited in an autosomal-recessive pattern.<sup>38</sup> Some support the classification of TYK2 homozygous mutation as a distinct atypical HIES with susceptibility to mycobacterium.<sup>39</sup> The prevalence of AR-HIES is less than 1 in 1,000,000<sup>40</sup> with some 130 affected families reported to date.

### **Pathogenesis**

AR-HIES is a combined immune deficiency where DOCK8 or TYK2 mutations affect CD4 and CD8 proliferation, B cells, and memory cells. Homozygous mutations of DOCK8 (9p24.3) result in its loss of function. DOCK8 belongs to a subfamily of guanine nucleotide exchange factors, which have multiple roles, including signal transduction and activation of small G proteins. Recent evidence suggests that, although T and NK cells home and migrate into human tissue normally, the cytoskeletal defects in DOCK8-deficient T and NK cells lead to an unusual form of cell death—"cytothripsis" (cell shattering).<sup>41</sup> The inability of effector T cells and the absence of memory CD8<sup>+</sup> T cells leave patients without protective immunity and a sensitivity to viral infection. Homozygous mutations in TYK2 (19p13) interrupt cytokine-controlled survival, proliferation, differentiation, and function of immune cells as well as others. This member of the JAK signaling family associates with the cytoplasmic domain of types 1 and 2 cytokines including interleukins, interferons, and hemopoietins by phosphorylating receptor subunits. Disruption of antiviral types 1 and 3 interferon signaling pathways lead to an increased susceptibility to viruses and mycobacterium.

### **Diagnosis**

Similar to AD-HIES, AR-HIES patients have elevated total white blood cell counts that do not increase with acute infection, eosinophilia, and IgE. There are usually low T-cell numbers, low serum IgM levels, and a failure to sustain protective titers against vaccination. Owing to variability of presentation, flow cytometry for T helper 17 cells may be low. Clinically distinct features differentiate STAT3 AD-HIES and AR-HIES (DOCK8 and TYK2) mutations, which help to guide the appropriate genetic testing (see [Table 2](#)). The gold standard of diagnosis is molecular sequencing of these genes. Prenatal diagnosis should be considered if there is a family history.

### **Differential diagnosis**

Other conditions to consider include severe eczema, AD-HIES, IPEX, HIV, Netherton syndrome, as well as SCID with skin graft versus host disease.

### **Management**

Aggressive treatment of infection is critical to the care of patients with AR-HIES. The prognosis is poor, with most failing to reach adulthood as a result of sepsis, neurologic

disorders, and malignancies. Vascular complications (aneurysms) have been documented, including those secondary to vaccine-strain varicella zoster.<sup>42</sup> HSCT may be curative but remains experimental.

## SUMMARY

The majority of patients with eczema, eosinophilia, and elevated IgE are likely to be atopic individuals that can be helped with some type of corticosteroid therapy. Oral corticosteroids have long been the mainstay of therapy to treat severe flares of allergic diseases. Direct binding of the glucocorticoid receptor complex to glucocorticoid responsive elements in the promoter region of genes, or by an interaction of this complex with other transcription factors such as activating protein-1 or nuclear factor-kappa- $\beta$  inhibit production of many proinflammatory cytokines, chemokines, arachidonic acid metabolites, and adhesion molecules while concurrently upregulating anti-inflammatory mediators.<sup>43</sup> But, patients with the PIDs described rely on the remaining functioning parts of their immune system to control latent infections and combat opportunistic diseases (*Pneumocystis jirovecii*, *Mycobacterium avium* complex, and fungi). The broad scope of immune suppression by administered corticosteroids can lead to detrimental effects if an underlying PID goes unrecognized.<sup>42,44,45</sup> The increased risk (178-fold) of severe disseminated varicella infection owing to recent exposure to systemic corticosteroids<sup>46</sup> has been debated<sup>47</sup>; nevertheless, practitioners should exercise prudence before using elective systemic corticosteroids or other immune suppressants if there is a history of recurrent or opportunistic infection(s). Although highly effective and beneficial in otherwise healthy immune competent individuals with allergic flares, immune suppression of immune compromised PID individuals can lead to life-threatening dissemination of infection(s).<sup>42,44</sup>

PIDs are rare diseases that can be masked or not considered because of the predominant clinical features of atopy. Without considering an underlying PID, some individuals will remain undiagnosed and untreated, and this risk impacts their morbidity and mortality, especially when exposed to agents that further reduce immune competence. An underlying PID should be considered especially in severe cases of atopic disease with concurrent signs of autoimmunity and unusual infections so appropriate treatment regimens can be initiated and inappropriate immune suppression avoided.

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