Primary Immune Deficiencies in the Adult: A Previously Underrecognized Common Condition

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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Learning objectives:

1. To describe the prevalence of primary immunodeficiency (PID) in the adult population.

2. To understand the long-term outcomes of PID and its various treatments.

3. To outline differences in PID presentation and management between adults and children.

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The large majority of classified primary immune deficiency (PID) diseases present in childhood. Yet, most patients with PID are adults, with a large proportion experiencing onset of symptoms beyond their childhood years. Most of these are diagnosed predominantly with antibody defects, but cellular and other disorders are increasingly being identified in older patients as well. Moreover, advances in clinical immunology are allowing pediatric patients, even those with severe disease, to reach adulthood. Because of differences in the physiology and pathophysiology of children and adults, the presentation, diagnosis, and management of a complex chronic disease could differ significantly between these patient populations and therefore require modifications in approach. **(J Allergy Clin Immunol Pract 2016;4:1101-7)**

Key words: *Primary immunodeficiency; Adults*

To date, more than 200 primary immune deficiency (PID) diseases have been identified and classified,[1] with most of these diseases usually presenting and being diagnosed in childhood. However, taken together, most patients with PID are actually adults—some are diagnosed as adults, whereas others are diagnosed in childhood and survive into adulthood. In either case, and as with any chronic disease, the management of a PID may significantly differ between adults and children, necessitating alterations in the diagnostic approach, follow-up strategies, monitoring techniques, and treatment modality.

Allergist/immunologists stand in the forefront of diagnosing and managing PID. Some cases are treated at the community level, whereas other—usually more complex—cases are referred to tertiary medical centers or dedicated academic PID centers. In either case, it is imperative that the practicing community allergist/immunologist possess maximal awareness of the broad scope of PID in the adult. Moreover, in some instances, the presentation of a PID in an adult may be complex and multisystemic. In such cases, even the initial referral to an allergy/immunology specialist may be delayed, with the patient being

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Abbreviations used
CGD- Chronic granulomatous disease
CVID- Common variable immune deficiency
HSCT- Hematopoietic stem cell transplant
IVIG- Intravenous immunoglobulin
PID- Primary immune deficiency

initially managed by a nonimmunologist. To expedite proper management of these patients, a deep understanding of the extent of PID in the adult must be established among nonimmunologists as well. Other reviews have focused on the approach to diagnosis of PIDs in adults[2-4] and this will not be reiterated here. This review will highlight recent epidemiological research regarding the prevalence of PID diseases in adults and focus on new findings unique to the adult with PID, emphasizing dissimilarity of PID in the adult from PID in the child. It will discuss the distinctive issues facing older patients and their physicians in the diagnosis and treatment of PID, whether the PID initially presents in adulthood or whether the PID is diagnosed in childhood and the patient matures into adulthood. The long-term, adult-age outcome of PID diagnosed in childhood will also be reviewed.

THE BURDEN OF PID IN ADULTS

Studies performed in the past decade have corrected common underestimations about the prevalence of PID in adults. These have demonstrated that the burden of PID in adults is not less than that in children. A study compiling and analyzing various national registries to extrapolate the worldwide prevalence of PID[5] has shown that although the estimated incidence of PID was highest in children (reaching 21.9/100,000 in the 0-4-year age range), overall 69.4% of all new worldwide PID cases are diagnosed at age over 15 years and more than 50% are diagnosed at ages over 25 years. In a telephone survey of American households,[6] it was found that of patients living with PID, more than half (57%) are older than 18 years. Reflecting this, a high percentage (>30%) of general internists practicing in the community will have encountered a subject with PID within a time frame of 5 years.[7] Moreover, if an adult is referred to a dedicated PID clinic (by an allergist/immunologist or other associated subspecialists) for assessment of a potential PID, the likelihood of identifying one is surprisingly high. In a Canadian study,[8] of 381 adult patients referred to the Immune Deficiency Treatment Center of the McGill University Health Center over a 10-year period, more than half (210) of the patients were found to have a PID. In an earlier study,[9] of 237 patients of all ages referred to the Mount Sinai Immunology Center, 113 were diagnosed with PID, and within this group, the mean age of diagnosis was 31.5 years. PIDs have been shown to exist in the elderly populations as well with an unexpectedly high prevalence. In the European Society for Immunodeficiency registry, 8% of all patients with PID are 65 years and older.[10] Even the very old may not be spared, with one report of a new diagnosis of common variable immune deficiency (CVID) in a 92-year-old man.[11]

Although much of the incidence of adults with PID is driven by predominantly antibody deficiencies,[1,12,13] rarer non−predominantly antibody deficiency entities can also present themselves in adulthood and must be taken into account. Moreover, the increasing survival of children with serious immunodeficiencies is expected to alter the distribution of PID classes in adults, making a scenario of an aging patient with a disease such as chronic granulomatous disease (CGD) or hyper-IgE syndrome more common. Taken together, it is clear that the distribution of PID subgroups in adult patients is dynamic and is expected to change over the foreseeable future.

DIAGNOSING PID IN ADULTS

Diagnosis of a PID beyond childhood generally occurs in 2 scenarios: the first is when the disease manifests only in later years. This can be further divided into PID diseases that usually present late in life and diseases that generally tend to be diagnosed in early years but on occasion do not present until adulthood (Figure 1).[14-40] The second scenario is when symptoms and signs do appear in childhood, but they have such poorly defined clinical and immunological phenotypes that the possibility of PID is not considered or explored.

A PID disease in which symptoms develop after a normal childhood is not uncommon. This occurs most commonly with predominantly antibody deficiency (and especially with diseases such as CVID and IgA deficiency) yet can occur with various cellular defects as well, although much less frequently. Interestingly, the latter category can include severe defects in cellular immunity with combined immunodeficiencies, such as late-onset combined immunodeficiency. The mechanism(s) underlying late expression of (mono) genetic mutation involving immune function is unclear, though various explanations exist. These include the existence of hypomorphic mutations, age-related thymic involution, age-related skewing in random X-chromosome inactivation, somatic mutations, and a possible requirement for concurrence of environmental factors for phenotypic expression.[41]

The more perplexing and challenging reason for the diagnosis of PID in adulthood is when the final diagnosis is deferred because of an atypical clinical and immunological presentation in childhood. Sometimes, this can simply manifest as mild recurrent infections that commence in early childhood with gradual worsening in frequency and severity as the patients age, until full presentation in adulthood leads to assessment and diagnosis. An example of such a condition is type 2 hyper-IgM syndrome with the R112C mutation of activation-induced cytidine deaminase, which tends to be diagnosed in later life because the childhood infectious disease history can be so mild as to not warrant an immune workup.[42] However, the childhood presentation might also be extremely complex and not necessarily include significant recurrent infections. Instead, various complex combinations of failure to thrive, chronic diarrhea, nonspecific dermatitis, autoimmune manifestations, or abnormal facies and other congenital defects are found, leading to the underrepresentation of PID in the differential diagnosis of these patients resulting in delayed diagnosis. Under these circumstances, diseases such as adenosine deaminase deficiency have been diagnosed in adulthood after years of workup for ill-defined clinical manifestations, including nonspecific dermatitis, frequent febrile convulsions, pneumonitis, hepatitis, furunculosis, and diarrhea. In these patients, novel heteroallelic missense mutations in the adenosine deaminase gene have been found.[23] In another example, MHC-1