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REVIEW

New paradigms in primary immunodeficiencies

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ABSTRACT

Primary Immunodeficiencies are characterized by a dysfunctional immune system, resulting in susceptibility to infections, autoimmune, allergic and malignant diseases. These entities are more common than generally believed. Nevertheless, there is not enough awareness about this topic among physicians. There is a gap between research and clinical practice. Many options are available for the patients, but as misdiagnosis is frequent, they do not have access to them. This increased morbidity and decreased quality of life and life span. Therefore, health care professionals should be informed about all the possibilities and developments in the matter.

Key Words: Awareness, immune system diseases, medical education, research.

Introduction

There are more than 200 disorders currently recognized as Primary Immunodeficiencies (PIDs), and estimated to rise with 3000 predicted diseases by 2021 [1]. Its true incidence or population prevalence either individually or in a group, is unknown. There is wide variation depending on geographic area, race, consanguinity, individual PID diagnosis, diagnostic centers distribution and access to local specialist services. Furthermore, PIDs are frequently under-diagnosed and under-reported [2-12]. A survey from the United States reported a prevalence of 1 in 1200 persons making them far more common than commonly believed [13]. Moreover, IgA deficiency, the commonest primary immunodeficiency, has an estimated prevalence of approximately 1 in 500 people [14]. Therefore, although PIDs are considered rare, physicians, both generalists and specialists, are likely to see persons with underlying PIDs in their practice [15].

In the past years, the field of PIDs has grown rapidly and significantly, but there is a gap between the progress of research and clinical practice [16-21]. Awareness about PIDs among health care professionals needs to be promoted, because lack of the knowledge translates directly into diagnostic delay, inadequate management with increased morbidity and mortality [22-27]. It is thought that 70% to 90% of PIDs patients in the world remain undiagnosed [28]. The objective of this review is to highlight recent advances in the PIDs field.

What is and what is not a PID?

There is no consensus about the definition of the term primary immunodeficiency [1,29]. But in accordance with its classification by the International Union of Immunological Societies (IUIS) Expert Committee on Primary Immunodeficiency and available knowledge in this subject, PIDs are a heterogeneous group of genetically determined disorders of the immune system. "Primary" refers to a disease caused by a mutated genotype and "immunodeficiency" reflects the existence of defects in the development, function or both of the immunity. Susceptibility to recurrent and severe infections is the most frequently noted clinical manifestation, but can include alternate presentations like severe allergies, autoimmune disorders, malignancies, chronic inflammatory states and congenital anomalies [Figure 1]. Although a hematopoietic-centered view of host defense is well known, extra-hematopoietic defects may be present and non-hematopoietic cells (such as keratinocytes, endothelial cells, fibroblasts, neurons and oligodendrocytes) are involved in the pathogenesis of many PIDs [1,15,30,31].

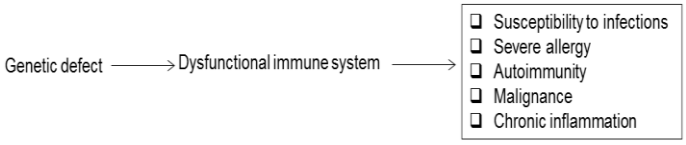

Figure 1 What is a PID?

In addition, characteristics of infection and susceptibility to microorganisms in PID depend of the underlying immune defect. Primary antibody deficiencies (PADs) are associated with bacterial infections of the sinopulmonary tract. T- cell or combined T- and B-cell immunodeficiencies predispose to opportunistic infections by viruses, fungi, bacteria and protozoa. Phagocytic disorders present with bacterial or fungal infections. Complement defects predominantly present with pyogenic bacterial infections, particularly Neisseria [32,33]. Besides, some PIDs confer vulnerability exclusively to a specific kind of microorganism, presenting with a single episode of infection in infancy with no recurrence [30,34]. Examples include IL-12R β1, IL-1 receptor – associated kinase 4 (IRAK-4), UNC-93B and TLR3 deficiencies [35-38].

Although PIDs are genetic diseases, they are not exclusively pediatric disorders and can manifest at any age from birth to adulthood. Common variable immunodeficiency (CVID), one of the most common PIDs, is an example frequently mentioned. Other PIDs with later onset are: pulmonary alveolar proteinosis and dominant IFN- γ R1 deficiency and even severe PIDs as X-linked agammaglobulinemia (XLA) and chronic granulomatous disease (CGD), typically of early

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onset, can vary in its age of presentation. Causes for adult cases of PIDs are diverse and include nature and location of mutations within the gene, age-related changes in X chromosome inactivation patterns and other poorly defined factors [39,40].

Genetic basis of PID are varied and include familial, sporadic, monogenic or polygenic, autosomal dominant or recessive, and X-linked subtypes. Mutations can be de novo, inherited, germline, somatic, of complete or incomplete penetrance, antimorphic (dominant negative), neomorphic, hypermorphic, hypomorphic or amorphic, heterozygous versus homozygous. Expression variability and interactions with environmental factors also contribute to the phenotypic diversity of PIDs [1,30].

Classification

As mentioned above, all components of the immune system can be affected in PIDs. These are classified into eight immunophenotypical categories [Table 1]. The IUIS PID Expert committee meets every 2 years since 1973 to update the classification of PIDs. The last document outlines the progress in the matter and the overlap in the immunophenotype between PIDs. A same disease can be classified in two categories. An example is autosomal recessive hyper-immunoglobulin E syndrome caused by DOCK8 (dedicator of cytokinesis 8) deficiency: belongs to combined immunodeficiencies and well-defined syndromes with immunodeficiency.

Table 1 Primary immunodeficiency diseases classification
Combined immunodeficiencies
Well-defined syndromes with immunodeficiency
Predominantly antibody deficiencies
Diseases of immune dysregulation
Congenital defects of phagocyte number, function, or both
Defects in innate immunity
Autoinflammatory disorders
Complement deficiencies

The research of PIDs has contributed enormously to understanding of the human immunity. New phenotypes associated to defects of immune system are described and a novel group of PIDs has emerged (31 newly diseases were added to the IUIS report), many due to investigation of pediatric idiopathic infectious diseases. Mutations that confer susceptibility to trypanosomiasis, mycobacterial infection, herpes simplex encephalitis (HSE), invasive pneumococcal disease, chronic mucocutaneous candidiasis (CMC), *Salmonella* and *Staphylococcus aureus*, have been detected [36,37,41-45] [Table 2]. It now appears that genetic background of host greatly determines the development of infections [34,46].

Warning Signs of PIDs

The Warning Signs (WS) of PIDs [Table 3] was created to facilitate early diagnosis of PIDs and to avoid complications associated with delayed treatment. Nevertheless, these are not evidence-based and do not take into account recent described phenotypes. Hence, there is a growing interest for to find stronger identifiers of PIDs in children [47,48].

Table 2 Mutated genes causing susceptibility to specific infections	
Trypanosomiasis	APOL-I
Mycobacterial infection (Mendelian susceptibility to mycobacterial diseases)	NEMO, IFNGR1, IFNGR2, STAT1, IL12P40, IL12RB1 and IRF8
Herpes simplex encephalitis	UNC93B1, TLR3, TRAF3 and NEMO
Invasive pneumococcal disease	NEMO, IRAK4 and MYD88
Chronic mucocutaneous candidiasis	CARD9, IL-17RA, IL-17F, STAT 1 and STAT3
Salmonella	IFNGR1, IFNGR2, STAT1, IL12P40 and IL12RB1
Staphylococcus aureus	NEMO, IRAK4, MYD88, TYK-2 and STAT-3

List of abbreviations:
Apolipoprotein L-I (APOL- I)
Nuclear factor-kβ–essential modulator (NEMO)
IFN-γ receptor 1 (IFNGR1)
IFN-γ receptor 2 (IFNGR2)
Signal transducer and activator of transcription 1 (STAT1)
IL-12 p40 subunit (IL12P40)
IL-12 receptor β-subunit (IL12RB1)
Interferon regulatory factor 8 (IFR8)
UNC93, C. Elegans, homolog of, B1 (UNC93B1)
Toll-like receptor 3 (TLR3)
TNF receptor-associated factor 3 (TRAF3)
Interleukin-1 receptor-associated kinase 4 (IRAK 4)
Myeloid differentiation factor 88 (MyD 88)
Caspase recruitment domain-containing protein 9 (CARD9)
Interleukin 17 receptor A (IL17RA)
Interleukin 17F (IL17F)
Tyrosine kinase 2 (TYK2)
Signal transducer and activator of transcription 3 (STAT3)

Table 3 Twelve warning signs of PIDs
Eight or more new ear infections within one year.
Two or more serious sinus infections within one year.
Two or more months on antibiotics with little effect.
Two or more pneumonias within one year.
Failure to thrive.
Recurrent deep skin or organ abscesses.
Persistent thrush on mouth or fungal infection on skin.
Need for intravenous antibiotics to clear infections.
Two or more deep-seated infections including septicemia.
A family history of PIDs.
Complications after infections.
Morbidity associated live vaccine.

MacGinnitie et al. did a retrospective analysis of 141 North American children evaluated for possible PID and found that promulgated WS had low specificity (23%) and relatively low sensitivity (63%) and did not distinguish between patients with and without PID. In addition allergies (an important differential diagnosis) frequently coexisted with some of these PIDs [49].

Subbarayan et al. undertook a retrospective survey of 563 children who presented to two pediatric immunodeficiency centers in England and compared 430 patients with a defined PID and 133 patients for whom detailed investigations failed to establish a specific PID. They determined that 3 WS were helpful for to diagnose children with PIDs. Positive family history (physician diagnosed PID in a family member) was

the strongest sign and the only able of to identify B - lymphocytes deficiencies. For neutrophil PIDs, use of intravenous antibiotics and for T- lymphocytes PIDs, failure to thrive. Using these three parameters, 96% of patients with neutrophil and complement PID and 89% of children with T-lymphocyte PID could be correctly identified. This group data promoted the need for education campaigns among physicians, especially hospital pediatricians, and families with history of PIDs [47].

On the basis of the results of both these studies, I believe that practitioners should have a low threshold for to assess immune function (principally antibody levels) in children with recurrent and / or severe infections. The key to detecting a PID is suspecting it. Moreover patients with PIDs must be referred for appropriate management to a sub-specialist [47,49].

Carneiro-Sampaio et al. call attention about the necessity to detect the most severe PIDs that manifest in very early in life, are really pediatric emergencies and require hematopoietic stem cell transplantation. Based on literature and their experience, they proposed 12 warning signs of PIDs in infants that include high susceptibility to infections, immune dysregulation, manifestations of autoimmunity, excessive inflammation, adverse reaction to live vaccines, congenital heart defects, delayed cord detachment, persistent lymphocytopenia or other cytopenia, hypocalcemia and absence of thymic shadow at x-ray. Aside from clinical signs, accessible and low-cost laboratory assays are taken into account [50].

Likewise, members of European Society for Immunodeficiencies (ESID) and other colleagues have updated the multistage expert opinion-based diagnostic protocol for non-immunologists incorporating newly defined PIDs. The multi-stage design allows cost-effective screening for PIDs. More expensive tests are reserved for a later stage requiring the participation of a specialist. The protocol is based on that PIDs tend to present in eight clinical patterns of signs and symptoms. This diagnostic strategy is a way to efficiently recognize PIDs, that can be used when clinical problems persist despite a normal initial evaluation or when initial examinations are compatible with PID [51].

Newborn screening

Timely treatment is life saving for many patients with PIDs, but challenges in diagnosis and paucity of knowledge confound this issue. In this regard, an important advancement in PIDs is the possibility of implementation of universal newborn screening (NS) programs [52-55].

Severe combined immunodeficiency (SCID) is a combined T and B- cell disorder that is fatal in infancy requiring prompt intervention. This is the first PID to be amenable to NS, and also the first NS tests for which the analyte is DNA. The outcomes in SCID are better when infants are diagnosed earlier. SCID and other conditions with low numbers of T lymphocytes (complete DiGeorge syndrome, partial DiGeorge syndrome with low T lymphocytes, CHARGE syndrome, Jacobsen syndrome, trisomy 21, RAC2 dominant interfering mutation, DOCK8 deficient hyper-IgE syndrome, cartilage hair hypoplasia) can be screened by quantification of T-cell receptor recombination excision circles (TRECs) with real-time PCR analysis of DNA (isolated from dried blood spots). TRECs are pieces of DNA cut during intrathymic T-cell receptor gene rearrangement and are a biomarker of normal T cell development indicating newly formed thymic-emigrant T cells. The frequency of TRECs-bearing T cells in peripheral blood diminishes with T cell expansion. Normal newborns have a high rate of new T cell production, resulting in TRECs numbers at about 10% of their total T cell numbers; in contrast older children and adults have progressively lower ratios of TRECs [56,57].

NS tests using TRECs have been successfully implemented in Wisconsin, Massachusetts, California, New York, Louisiana and Puerto Rico and are starting to be used in Colorado, Connecticut and Michigan in the United States [57,58].

Prognosis and therapeutic options of patients with PIDs

Patients with PIDs do not always have bad prognosis. Some of these diseases have a favorable outcome with no relapses. [30] Alternately patients with severe diseases (for example, Wiskott–Aldrich Syndrome-WAS) have had revertant mutations and then are able to express functional protein [40,59].

Nonetheless, timely treatment is the principal determinant of the prognosis [54,55,60,61]. There are different therapeutic options for these patients: replacement with immunoglobulin intravenous or sublingual (especially for patients with PADs), cytokine therapy (principally for distinct types of neutropenia and other diseases with phagocytic defects], stem cell transplantation and gene therapy (has been studied in SCID caused by an adenosine deaminase defect and other forms of SCID, WAS, CGD), among others [62-66]. Additionally these patients need appropriate prophylaxis and antibiotic therapy, special vaccination regimen, nutritional and psychological assistance, genetic counseling and familial support [67-69].

One of the most promising discoveries in the field of treatment of PID are Induced Pluripotent Stem Cells (IPSC), stem cells generated from adult cells (for example, fibroblasts). These permit the development of disease models and can serve as a platform for workup and optimization of new strategies of treatment, principally those based in genetic correction. However, it needs to improved techniques and address many ethical and biosafety dilemmas [70,71].

Resources

Various scientific communities and patient groups, researchers and health professionals are dedicated to the field [Table 4] and have been built patients registries on every continent providing valuable information about demographic, clinical and laboratory characteristics of PIDs. This data is vital for planning services and health programs and for improve patient care [72].

Additionally, databases of mutations and molecular alterations are available which make it possible to elucidate

the pathophysiology of these diseases and facilitate the accurate diagnosis of patients [73,74]. Molecular analysis and genetic testing are useful in characterizing the role of molecules in cellular function, confirming the clinical diagnosis, identifying new genetic defects or atypical presentations of PIDs, assisting treatment decisions, supporting classification of PIDs, for urgent diagnosis in infancy where conventional diagnostic tests are unreliable and prenatal diagnosis and early identification of disorders that present later in childhood. However, genetic testing is not available for all PIDs [40,75,76].

Table 4 Primary immunodeficiencies resources

Jeffrey Modell Foundation	http://www.info4pi.org/
Immune Deficiency Foundation	http://www.primaryimmune.org/
International Patient Organisation for Primary Immunodeficiencies	http://www.ipopi.org/
ImmunoDeficiency Resource	http://structure.bmc.lu.se/idbase/IDRefSeq/idr/index.shtml
European Society for Immunodeficiencies	http://www.esid.org/
Latin American Society for Immunodeficiencies	http://www.lasid.org/
Resource of Asian Primary Immunodeficiency Diseases	http://web16.kazusa.or.jp/rapid/ /
African Society for Immunodeficiencies	http://www.asid.ma/
IDbases	http://structure.bmc.lu.se/idbase/
Primary Immunodeficiencies Medical Education Program	https://sites.google.com/site/pemidp/english

Conclusions

The field of PIDs has grown enormously in the last many decades, but the awareness of health providers has not increased in parallel. I advocate for greater education of clinicians to be of timely and appropriate service to this special subset of patients.

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Competing Interests

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