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From Primary Immunodeficiencies (PID) to Inborn Errors of Immunity (IEI): How Much Progress Have We Made in Understanding the Immune System Defects

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ABSTRACT

Primary immunodeficiencies (PIDs) have traditionally been defined as a precondition for increased susceptibility to infections, and the global prevalence is currently estimated to be 1:10,000 people. While data is increasing, as are diagnostic tools, some conditions still do not fit within the range of clinical manifestations, and to capture more accurately, the term "innate immunity errors" (IEI) has been proposed, which has allowed a more complete analysis of the associated defects, so in this mini-review we will discuss the advances in the study of PID under this new approach.

Keywords: Primary immunodeficiencies, Innate immunity errors, CGD, Chediak Higashi

ABBREVIATIONS

PID: Primary immune deficiencies; IEI: Innate immunity errors; CGD: Chronic Granulomatous disease; SCID: Severe Combined Immunodeficiency; AR: Autosomal recessive; LOF: Loss of function; GOF: Gain of function variations; PAD: Primary antibody deficiencies

INTRODUCTION

Primary immunodeficiencies (PID) have traditionally been defined as pre-conditioning to a greater susceptibility to infections, due to genetic defects that affect both the development and the functioning of the different elements that make up the immune system. The first description was made by Bruton [1] who described a child who had suffered more than 15 episodes of pneumococcal infections, lacked serum immunoglobulins (Igs) and recovered with Igs administration. Later was reported other infants with life-threatening early-onset infections that lacked immunoglobulins, and also has absence of lymphocytes (T and B) [2], suggested a Severe Combined Immunodeficiency (SCID) provided evidence the role of humoral and cellular immunity in protecting against infection [3]. Next, was reported a patient with recurrent infections and, paradoxically, elevated serum immunoglobulins, a condition designated as chronic granulomatous disease in 1957 [4], after where multiples report has been enrichment the literature on immunodeficiency field. Our group in Venezuela has been published several findings in the field of PID, one of the first reports was the description of foci in the Venezuelan Andes of Higashi [5] and CGD [6,7] associated with high inbreeding, and recently we reported during thirty-two new cases of PIDs in pediatric patients [8]. It was soon recognized that the nature of the pathogens (viruses, bacteria, fungi or parasites, "opportunistic" or not) that cause infections in PID patients is largely determined by the affected immunity arm (T lymphocytes, B lymphocytes, phagocytes and complement). Therefore, patients with PID are more often susceptible to infections and immune dysregulation than be associated with severe allergies, autoimmunity or autoinflammation, cancer susceptibility, or complex integrated syndromes affecting different organs and systems, including developmental disorders, epilepsy, disability intellectual, autism, gastro enteropathy, dermatosis, pneumopathy and skeletal abnormalities, among other clinical events.

The estimated prevalence worldwide is 1: 10,000 individuals, however data that is increasing, especially due to advances in knowledge, diagnostic tools and the high rate

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of inbreeding in certain communities. Currently the global EPI registries indicate that there are 104,614 patients [9] and the Jeffrey Modell Centers Network (JMCN) shows 187,988 patients [10]. Both agree that Primary antibody deficiencies (PAD), are around 48,5% and Combined immunodeficiency, are around 8,95%. The number of affected men is greater than that of women (5 vs. 1.3), highlighting X-linked disorders. When there is consanguinity, the frequency of autosomal recessive (AR) increases [10] and, with rare exceptions, PADs these are not obvious at birth, but become evident when the affected individual is exposed to pathogenic microorganisms and develops a recurrent or chronic infection or responds to antigens. with dysregulation of immune function causing severe allergy, autoimmunity, inflammation, lymphoproliferation, and malignancy [11]. As the immune system has high connectivity with all tissues, it is natural that the infectious and non-infectious manifestations of the genetic errors of the immune system, can manifest themselves in any tissue, such as: hematopoietic, gastrointestinal, respiratory, osteoarticular, muscular, cutaneous, central nervous system and peripheral nervous system and at any age. In this sense, the pediatrician has the possibility of being the first to suspect a primary immunodeficiency through family history, infectious history, the number of neutrophils and lymphocytes, the image of the thymus, and in general the opportunities for this suspicious diagnosis they continue with each visit to the care clinic.

"Inborn errors of immunity" (IEI)

Perhaps more than in other medical disciplines, the field of PID is expanding more rapidly thanks to recent advances in sequencing, gene editing tools, and the introduction of new biologics and molecules that target specific checkpoints relevant to immunity. However and despite the advances that have been made in recent years, some conditions still do not fit within the range of clinical manifestations, and to more accurately capture this wide range of phenotypes associated with these disorders of PID, the term "Innate immunity errors" (IEI) have recently been proposed as a complex group of diseases that cause quantitative and / or functional alterations in the elements of innate and adaptive immunity and manifest as increased susceptibility to infectious, autoimmune diseases, autoinflammatory diseases, allergy, and / or malignancy. Inborn errors of immunity are listed: combined immunodeficiencies, combined immunodeficiencies with syndromic features, predominantly antibody deficiencies, immune dysregulation diseases, congenital phagocyte defects, defects in intrinsic and innate immunity, autoinflammatory diseases, complementary deficiency errors, and phenocopies congenital immunity to errors. These conditions are caused by germline monogenic mutations that result in loss of expression, loss of function (LOF; amorphous/hypomorphic), or gain of function (GOF; hypermorphic) of the encoded protein. The use of next-generation sequencing has allowed the identification of an increasing number of IEIs, numbering 431 in the 2020 classification of the Committee on Inborn Errors of Immunity of the International Union of Immunological Societies [12]. It showed that most IEIs can be caused by mutations in different genes, which typically govern a certain pathway. Different pathogenic variants at the same locus have also been shown to cause different forms of IEI, but not necessarily due to different genotypes: mono-allelic versus biallelic lesions, loss of function (LOF) (or hypomorphic) versus gain of function variations (GOF) (or hypermorphic), and dominant-negative mode versus haplo subdomain [13].

Therefore, thanks to the increased availability of DNA sequencing and improve interpretation of genomic, newly identified genes associated with IEI have increased. Remarkably, the improved ability to define the pathophysiology of IEI at the molecular level has laid down the foundation for the development of targeted therapeutic interventions, based on the use of small molecules and biologics to target a specific cellular function. Advances in molecular biology tools have been beneficial in the field of clinical immunology and have allowed the addition of new genetic defects underlying inborn errors of immunity, and a large part of these new variants have been identified by Next Generation DNA Sequencing (NGS), that allow the application of efficient sequencing, using panels of specific genes, complete exomes or complete genomes to cohorts of patients suspected of having a monogenic alteration associated with their disease, thus highlighting that whole exome / whole genome sequencing has become the gold standard for identifying new variants of pathogenic genes. The application of these tools has allowed the updating of the list of immune diseases to 404, with 430 known genetic defects identified as causing these conditions. For example, has been shown that biallelic mutations in ZNF341 [14], or IL6R [15], cause conditions that resemble autosomal dominant hyper-IgE syndrome [16]. Other examples describe as dominant negative heterozygous mutations, are TCF3, encoding transcription factor E47, cause B cell deficiency and agammaglobulinemia [17-19], nonsense mutations in TCF3, that are pathogenic only in an autosomal recessive state, have now been identified as carriers of heterozygotes for these allelic variants and they remained healthy [20]. Another example is the biallelic LOF mutations in PIK3CD, which cause B-cell deficiency and agammaglobulinemia, but is quite different from the dysregulated immune status of individuals with activating mono-allelic PIK3CD mutations [21].

CONCLUSION

The discovery and study of innate errors of immunity has shown that more than 20% of these immune genes perform non-redundant roles in host defense and immune regulation. With improved identification and phenotyping of rare disease patients, combined with high-throughput genome sequencing, the number of genes required for immunity will

continue to increase, revealing even more critical and novel functions for genes, specific molecules, pathways and cell types in immune responses, as well as in the pathogenesis mechanisms of the disease and the goals of immunotherapies. Thus, the field of immunity inborn errors and the global research and clinical communities will continue to provide key insights into basic and clinical immunology. Finally, PID/IEIs will continue to show us about the underestimated complexity of our immune system.

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