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Primary Immunodeficiency Diseases in Latin America: Epidemiology and Perspectives

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1. Introduction

Primary immunodeficiencies (PID) are genetic disorders of immunity whose incidence varies from 1:250 to 1:1,000,000 depending of disease and study population. Because of incomplete records of immunodeficiency in the world, is estimated that the prevalence of 1:5,000 to 1:100,000 (Geha *et al.,* 2007; Boyle & Buckley, 2007; Notarangelo,*et al.,* 2010). Thus, the PID is a important group to public health as other genetic diseases that rely government support in a neonatal screening program such phenylketonuria (PKU) with incidence of 1/15.000 (de Carvalho *et al.*, 2007) and congenital hypothyroidism, with incidence of 1/4.000 (American Academy of Pediatrics, 1993; Olivieri, 2009). The PID are classified in defective immune deficiency prevalent in predominantly antibody; combined immunodeficiencies, cellular immunodeficiencies, phagocyte defects, immune deficiencies associated with lymphoproliferative diseases, and deficiencies of complement system or secondary immunodeficiencies associated with other diseases. This classification is updated periodically by the International Union of Immunological Societies (IUIS), associated with the World Health Organization (WHO) (Geha *et al.,* 2007; Notarangelo,*et al.,* 2010).

This classification is progressively adjusting to the rapid evolution of the field. Many new phenotypes (e.g. hemophagocytosis, thrombotic purpura, herpes encephalitis, Mendelian susceptibility to mycobacterial infection, epidermodysplasia verruciformis, chronic mucocutaneous candidiasis, autoinflammatory disorders, and anhidrotic ectodermal dysplasia with immunodeficiency) have emerged as reflecting new PID.

Knowledge of PID is still deficient in many countries and within many countries, since doctors and health authorities are often poorly informed about their clinical presentations, diagnosis, importance and health impact of these diseases, and geographic factors that influence the release of same around the world (Sewell, 2006). Recent estimates of PID made by the European Parliament showed that approximately 1 in 800 to 10,000 people have PID that significantly affects your health, PID affect at least 10 million people worldwide, the true prevalence of PID in some forms of general population is estimated between 1 in 250 and 1 in 500, data comparable with type I diabetes (1 in 700) and multiple sclerosis (1 in

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1000), although more than 200 PID have been discovered, some are more common than leukemia and lymphoma in children (Banks, 2010).

Initial efforts in classification of PID left WHO in 1970, where this first meeting was identified and classified 14 different entities, and in 2006, more than 100 types (Bonilla & Geha, 2006). Currently, they comprise more than 200 different types of genetic diseases that predispose the human host to recurrent infections, which may be associated with other disorders (Notarangelo *et al.,* 2010), but also to chronic and systemic inflammation, hypersensitivity reactions, autoimmunity, and cancer. Advances in biological sciences and biotechnology are now making possible for the first time, to systematically assess the actual impact of PID in human health, and this promises to revolutionize the way we look at these diseases.

Patients with PID have higher susceptibility to infection often accompanied by inflammatory disorders, hypersensitivity reactions, autoimmunity and cancer (Morimoto & Routes, 2008; Notarangelo 2010). The clinical presentation of patients is extremely broad, with asymptomatic individuals who have fulminating infection, which if not diagnosed and treated properly evolution to death (Chapel 2005; Bustamante *et al.,* 2008a). Patients with PID have consequence of delay diagnosis and treatment permanent damage of body. This involves disabling from attending school and/or work, reducing the number of people with productive capacity, increasing the number of people hospitalized with high cost to government, increased mortality rate in children and adults of working age (Yarmohammadi *et al.,* 2004; Bonilla *et al.,* 2005). The delay in diagnosis leads to pulmonary complications such bronchiectasis and irreversible change in the quality of life of patients and their families (Kainulainen *et al.,* 2001; Champi, 2002).

Although this delay in diagnosis of PID is evident in countries or disadvantaged regions, also occurs in developed countries after multiple hospitalizations of patients. Thus, is recommended research and education in PID, since the prognosis of many patients can be improved by early diagnosis and appropriate access to care and treatment (Bonilla *et al.,* 2005; Turvey & Bonilla, 2009). In medical terms, there are three important reasons for understanding the PID, first, a high index of suspicion and early diagnosis may lead to treatments that save lives or bring significant improvement in quality of life, secondly the discovery of genetic defects in immunity makes possible family counseling and prenatal diagnosis, and thirdly, the study of the pathophysiology of genetic and immunological defects provides important tools to understanding the regulation of the human immune system (Bustamante *et al.,* 2008b; Casanova *et al.,* 2008; Lee & Lau, 2009; Fried & Bonilla, 2009). In recent decades, no other field of immunology had so much progress in understanding how pathophysiology of primary immunodeficiencies. These developments have resulted not only in understanding of immunodeficiencies, but understanding of immune system in humans (Boufisha *et al.,* 2010). Patients with PID are considered not successful experiments of nature that brought many benefits to medicine in the installation of diagnostic protocols and rational treatment, location of targets for gene therapy and assessment of need for bone marrow transplantation and its benefits (Griffith *et al.,* 2009; Neven *et al.,* 2009; Pessach *et al.,* 2009; Kohn 2010). This knowledge was translated into association of specific defects of immunity with signs and symptoms that can establish correct diagnosis of disease, beyond the description of new immunodeficiency (Cassimos *et al.,* 2010). Since the PID diseases are congenital and hereditary character, children are

overweight patients, however, a greater number of adults have been diagnosed as children grow and become adults (Bustamante *et al.,* 2008a). How healthy children have on average 6-8 mild respiratory infections, especially upper airway in first year of life and more than six episodes of otitis and gastroenteritis per year in the first three years of life, young children with high environmental exposure or with siblings who attend schools may exceed these averages by one to two years, the diagnosis of PID is often underestimated (Puck, 1997). But they may be observed in children with normal development, which may harbor latent PID or low impact on the immune system. Pediatrics specialize in PID ensure that half children are taken by parents to the doctor with a history of recurrent infections are normal, and other 50%, 30% have allergies, 10% other diseases and 10% PID (Grumach *et al.,* 1997). To aid diagnosis and reporting of PID, the American Red Cross and Jeffrey Model Foundation developed the 10 warning signs suspected for PID. For experts (Modell, 2007a; Modell, 2007b), these signs are considered extremely important, since the prognosis and therapeutic success depends upon prompt diagnosis, and most are performed in referral centers. However, some authors consider the 10 warning signs not sensitive or specific, since a third of patients do not present single warning sign (Aloi *et al.,* 2007). Once diagnosed with PID, the patient is referred to clinical immunologist who directs specific treatment, immunizations, and definitive and specific diagnosis. Thus, there is a gain in quality life of patients and their families, avoiding sequels, unnecessary suffering and high social cost. The therapeutic treatment these patients involve three basic tenets: reduce the exposure to the infectious agent, effective or prophylactic antimicrobial therapy, replacement of deficient immune functions (Garcia *et al.,* 2007). During the evaluation of PID is essential documentation of the patient's clinical history, frequency, duration and complications of infections, outbreaks of infection, microorganisms involved and response to treatment, and anatomical defects, allergic processes and metabolic disorders (Bonilla *et al.,* 2005). A detailed family history should be taken into consideration, since many PID are linked with X chromosome and the presence of children in maternal family with recurrent infections, or death in childhood due to severe infection indicates the possibility of PID. Initially, screening tests are indicated or initial and advanced testing as suspected PID (Sewell *et al.,* 2006). In general, immune assessment requires specialized laboratory and high financial cost, and it comes to pediatric patients, should be chosen methods that can be executed with low amount of blood (Oliveira & Fleisher, 2010). The diagnosis of some PID may be removed if they are used and selected screening tests such blood test for congenital neutropenia, leukocyte adhesion deficiency (LAD), severe combined immunodeficiency (SCID) and Wiskott-Aldrich Syndrome (WAS), or immunoglobulin's quantification in suspected predominantly antibody defects (Gill, 2002). The diagnostic criteria are divided into three categories, definite, probable and possible. In ensuring inclusion of patients with polymorphic variants in genes associated with PID and specific clinical and laboratory changes, the patient must meet all criteria characteristic of the disease (Conley *et al.,* 1999). The delay in diagnosis is often associated with limited access to specialized resources (Lindegren, 2004), is not unique to developing countries (Liang *et al.,* 2008), leading to large variation between numbers of cases (Stihem, 2004). In Finland, the common variable immunodeficiency (CVID) showed delay time diagnosis of 5 years in 2/3 of patients and 10 years in 1/3 these (Kainulainen *et al.,* 2001), in United Kingdom this delay was 6.2 years during 1989 to 1995, and decreased 3.5 years after implantation of government program to guide distribution of national guidance on recognition and diagnosis of PID, after a study

conducted between 1996 to 2002 (Seymour *et al.,* 2005). To be assured diagnostic quality indicators should be generated which include patient registration data, which together form the field and field set and its variables called record. These cases are based registry designed to improve patient care, but are useful for studying diseases. An example is early records of 368 patients with chronic granulomatous disease (GCD) by American Foundation for Immunodeficiencies started in 1993, allowing a calculation of incidence of the disease for USA born in 1/200.000 (Winkelstein *et al.,* 2000). In 1997, this study has been expanded to Common Variable Immunodeficiency (CVID), Wiskott-Aldrich Syndrome (WAS), Severe Combined Immunodeficiency (SCID), Leukocyte Adhesion Deficiency (LAD), DiGeorge Syndrome, Hyper-IgM Syndrome (HIGM) (Winkelstein *et al.,* 2003) and X-Linked Agammaglobulinemia (XLA) (Winkelstein *et al.,* 2006), showing concern in development systems of records, population data for estimating incidence, prevalence and characteristics of disease. These data are important to maintain epidemiological studies and research and design of new clinical trials, reducing mortality, increasing survival and improved quality of life. In Europe, this service is performed by European Society for Immunodeficiency-ESID non-governmental organization that aims, to facilitate exchange of information between doctors, nurses, researchers, patients and their families, promote research into causes, mechanisms and treatment of PID (Sewel *et al.,* 2006; de Vries, 2006; Guzman *et al.,* 2007; Gathmann *et al.,* 2009). This group was established in 1993, Society in 1994, and receives data from 66 specialized centers in 26 European countries. In 2005 record showed amount of 10,000 patients from 26 countries with prevalence of 4-47/1.000.000, and the European internet-based patient and research database for primary immunodeficiencies results in 7,047 patients with PID in 30 countries (Knerr *et al.,*2008) and 7430 patients from 39 countries have been documented in the ESID database (Gathmann *et al.,* 2009).

In Latin America in 1993, was created the Latin American Group for Immunodeficiencies (LAGID) to study the prevalence of PID in different regions of Latin America and promote awareness of these diseases. There are also databases online with identification of mutations locus in specific cases of PID that are established by ESID and extended by others researchers. This was initiated in 1995 to collect data in Bruton's tyrosine kinase mutations (BTK) in XLA (Lindegren *et al.,* 2004). This occurred in Brazil, through the creation of Brazilian Group of Primary Immunodeficiencies (BRAGID), which through information campaigns, increased the number of 314 cases in 2000 to 536 cases in 2004 with Southeast region responsible for 70% total cases. Another relevant factor in understanding the epidemiology of PID is introduction of specialized care networks. In England there is the National Specialist Advisory Group Comissionary (NSCAG) of National Health System (NHS), which tracks PID complex cases, such the Great Ormond Street Hospital (Jones & Gaspar, 2000) and Newcastle General Hospital (Slatter & Gennery, 2010).

Several international initiatives are currently underway to promote awareness PID and increase number of diagnosis and registration of PID (http://www.primaryimmune.org/resources/resources.htm) (Modell, 2007a; Modell, 2007b; Pickett *et al.,* 2008). Considering the increasingly frequent recognition of these diseases and their valuable contribution to understanding human immune system and mechanisms of defense against infections (more frequent medical care in worldwide) (Alcais *et al.,* 2009), it is essential establish the frequency and type in population (Casanova & Abel, 2007; Ballow *et al.,* 2009). The lack of proper diagnosis and treatment are the main problems in patients with PID in Latin America. These are related to lack of proper training of pediatrics, leading to misdiagnosis or late diagnosis, lack of proper screening, lack of government resources to implementation

of diagnostic centers and disinterest of private institutions in diagnosis of PID, regional variability access to educational program and establishment of diagnostic and treatment center (Pickett *et al.,* 2008; Condino-Neto *et al.,* 2011; Leiva *et al.,* 2011).

2. Difficulties in diagnosis, treatment and education of PID in Latin America

2.1 Argentina

The main diagnostic centers in Argentina are located in Buenos Aires, and other centers are located in La Plata, Rosario, Cordoba and Mendoza. These centers are accessible and without cost to the community, provided that patients are referred by doctor. Private hospitals in Argentina offer only partial diagnosis, because no they have laboratories and professionals specialized in PID. Patients in Paraguay, Bolivia and Uruguay are also diagnosed and treated in Buenos Aires since these countries do not have adequate support. As their countries do not encourage their costs, or they do not have health insurance, this burden financially immunology centers in Argentina (Maceira *et al.,* 2010). Patients with PID who need IVIG are usually met in Buenos Aires, and treatment is not automatically continued in the pediatric patient who came into adults, it should be transferred from pediatric hospital to hospital for adults, interrupting treatment (Krasovec *et al.,* 2007). In Argentina, immunologists are not recognized experts by the Ministry of Health, and only two hospitals in Buenos Aires offer scholarships programs and post-graduate training in immunology funded by government agencies (Galicchio *et al.,* 2010; Condino-Neto *et al.,* 2011).

2.2 Brasil

It is estimated that Brazil has 2,000 patients on treatment and approximately 20,000 patients with PID (Leiva *et al.,* 2007). Immunological diagnosis is supported by numerous centers located in São Paulo, Minas Gerais, Paraná, Rio Grande do Sul, Bahia and Rio de Janeiro (Grumach *et al.,* 1997; Leiva *et al.,* 2007). Centers located in southeast of country have specialized researchers, structure and molecular diagnostics. In Brazil, the federal government assists the movement of patients from regions without infrastructure to specialized centers, and coverage for certain screening tests of PID (Ocké-Reis & Marmor, 2010; Paim *et al.,* 2011). High costs and access to specialized laboratories are considered major problems by doctors for the diagnosis of PID (results available http://www.bragid.org.br/download/graphicos.pps), with strong educational, whose website presents PID centers throughout Brazil, journals, reviews and articles, case discussions, and announcements of meetings. This is supported by St. Jude's Hospital children and government agencies FAPESP and CNPq. Activities of this group include completion of first and second Summer School of PID by LAGID, implementation of Electronic Registration of Latin America Immunodeficiencies (http://imuno.unicamp.br:8080/) with installation of hardware in UNICAMP center computing support of ESID. The Federal University of São Paulo-UNIFESP, in partnership with Jeffrey Modell Foundation and Baxter International, created the first Jeffrey Modell Diagnostic Center for PID in Latin America; with goal of enabling physicians perform diagnostic, treatment and education of patients and PID cases reported in Brazil and Latin America. Patients with PID who need IVIG in Brazil receive government financial support, and not institutions or private health insurance, where patients should be initially admitted for diagnostic and treatment center. In Brazil, there are numerous funding agencies to residency

programs in allergy and immunology, although only few centers are able to train professionals and PID treatment, located in São Paulo (Costa-Carvalho *et al.,* 2011; Condino-Neto *et al.,* 2011).

2.3 Chile

The best laboratories for diagnosis of PID in Chile are located in Santiago, Temuco, Valparaiso and Concepcion. Initial screening tests for PID can be performed in large hospitals, although it does not receive government financial support (Goic & Armas, 2010). As in most underdeveloped countries in Latin America, the diagnosis of PID is often performed after numerous episodes of infection and treatment, and patient referral to specialist in infectious diseases, and finally to immunology center. Patients with PID, who need IVIG, are not reimbursed by the public health system for PID, burdening the costs to patients, which makes the treatment is not performed or interrupted. Chile has a three-year residency in immunology at the University of Santiago of Chile, providing training care of adult and pediatric patients (Condino-Neto *et al.,* 2011).

2.4 Colombia

Colombia has a national PID referral center located in University of Antioquia in Medellin, which has laboratory equipped to perform molecular and immunological diagnosis of PID, and other centers and programs are being developed in Bogota, Cali, Cartagena and Barranquila. Currently, 80% of cases of PID in Colombia come from Antioquia (Montoya *et al.,* 2002; Obando *et al.,* 2005) and neighboring states, which represents less than 20% of Colombia population. Most clinical laboratories in Colombia are able to perform initial PID screening, but specific tests are only available in Medellin and Bogota (Montoya *et al.,* 2002; Diaz *et al.,* 2008). In Colombia, the government Compulsory Health Plan (POS) provides basic coverage for PID and additional coverage can be obtained from private insurance companies (Gonzáles *et al.,* 1999; Cardona & Segura, 2011). Patients with PID, who need IVIG, are not refunded by POS, but IVIG treatments are covered by private insurance companies, who refunded through government's national fund FOSYGA. In this country there is Foundation for Diana Garcia de Olarte PID, which supports and develops educational programs, provides infrastructure for IVIG treatment centers and offers legal advice for patients who need IVIG (Montoya & Sorensen, 2001). The University of Antioquia in Medellin has immunology program for medical residents, and like Latin American countries, this prefer specialize in other areas, since the financial return is greater (Condino-Neto *et al.,* 2011).

2.5 Honduras

Honduras has two PID diagnostic centers, located in Tegucigalpa and San Pedro Sula, accessible to entire community, first laboratory support specific PID, and country have serious problems in laboratory diagnosis and access costs (Leon, 2003), availability of IVIG and cost. Only two hospitals in Tecigalpa, including National Institute of Social Security, provide treatment with IVIG. The country has no specific PID program residency, and receives training only three months on basic immunology, autoimmunity, allergy and immunodeficiency (Condino-Neto *et al.,* 2011).

2.6 Mexico

Mexico has specialized centers diagnosis of PID in Mexico City, Monterrey and Guadalajara, and molecular diagnosis of some PID can be performed only in Mexico City. Mexico has serious access problems to laboratory tests, cost and medical education in PID (Romero-Márquez & Romero-Zepeda, 2010; Yavich *et al.,* 2010). The Access to IVIG is extended to public health system and is administered in public hospitals and clinics, but doctors do not follow specific guidelines for the administration of IVIG. The use of IVIG represents 20% of coast in obtaining drugs by National Institute of Pediatrics in Mexico City. In Mexico, there are plenty residency programs in allergy and immunology, with emphasis on allergies. Only the National Institute of Pediatrics in Mexico City has residency program with emphasis on pediatric allergy and immunology (Condino-Neto *et al.,* 2011).

3. Latin American group of immunodeficiency

One of major problems of records diseases in underdeveloped countries has been limitation of diagnostic and treatment, and send reports of cases by physicians, resulting in overestimation in certain clinical centers in collection of samples, since most of these centers is reference to some types of PID, and lack of standardized definitions of cases makes it impossible to calculate rates of healthy population from this source, by only reporting positive cases without reference population data (Condino-Neto *et al.,* 2011).

The PID diagnosis is performed in immunology centers, usually located in major cities of Latin American countries, and the vast majority of pediatricians and general practitioners are not prepared to establish PID diagnosis. The medical community educator has a role in awareness of population and health professionals in PID. In 1997, the University of São Paulo, Brazil, 166 cases of PID were registered with frequency of predominantly humoral defects (60.8%), T cell defects (4.9%), combined T-and B-cell deficiencies (9, 6%), phagocyte disorders (18.7%) and complement deficiency (6%). During observed period, 13.8% of children died, primarily of recurrent infections. In comparison with other reports, was higher relative frequency of phagocyte and complement deficiency. This is the first report on PID over 15 year's observation (1981-1996) (Grumach *et al.,* 1997). In 1998, a Colombia study with 83 PID patients demonstrated most common disturbance was antibody deficiency (74,6%), followed abnormalities of unspecific mechanisms (13,3%), deficiencies of cell mediated immunity (9,6%), and mortality ratio was 6% especially in patients with cellular deficiency (Núñes, 1988).

In Antioquia, Colombia, between August of 1994 and July of 2002, 98 patients was registered with diagnosis of PID, with most frequent report antibodies deficiency (40,8%), followed by combined deficiencies (21,4%)(Montoya *et al.,* 2002). In Latin America, in 1993, immunologists from four Latin American countries (Argentina, Brazil, Chile, Colombia), created the Latin American Group for Immunodeficiencies (LAGID) to study the frequency of PID and promote knowledge by general practitioners and specialists in allergy and immunology, including Latin American countries, creating a record in each participating country. Currently, 14 countries belong to this group, which had record 3321 patients in 2004.

LAGID was implemented in 1993 with the mission to include several Latin American countries, spread the educational and awareness programs, establish PIDD registries, and

promote annual scientific meetings with the participation of well-recognized international authorities in the PID field, This environment made possible the intensive interaction among Latin American doctors which in turn interacted with North American and European investigators resulting in a network, significant scientific development in Latin America, and the several resultant publications, starting with the clinical studies based on the LAGID registries

In order to encourage the registration of cases by LAGID, this sets out on its website (http://www.lagid.lsuhsc.edu) the objectives:

1. Knowing the frequency of different PID
2. Compare the frequency of different PID by region and country
3. Knowing the time that elapses between the onset of symptoms and diagnosis and measure whether this time can be shortened through the dissemination of knowledge about PID
4. Create awareness in importance of PID in primary care physicians, educators from basic and clinical science and health authorities to decide how to allocate resources for diagnosis and treatment of diseases in diverse groups
5. Promote research in various aspects of specific PID that would not be possible to settle in very small groups of patients
6. Disseminate the findings in field of Latin American PID to medical and international immune community
7. Facilitate the formation of support groups for parents and sponsors

The first LAGID published a series of studies in 1998, recording instances of medical services totaling 1428 patients of eight countries (Argentina, Brazil, Chile, Colombia, Costa Rica, Mexico, Paraguay, Uruguay), concluding that predominantly antibody deficiencies were reported in 58% patients, followed by cellular and antibody immunodeficiencies associated with others abnormalities in 18%, immunodeficiency syndromes associated with granulocyte dysfunction in 8%, phagocytic disorders in 9%, combined cellular and antibody immunodeficiencies in 5%, and complement deficiencies in 2% of patients (Zelazko *et al.*, 1998).

In a second step, this same group published a second series of studies in 2007, documenting 3.321 cases of 12 Latin American countries (Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, Mexico, Peru, Paraguay, Uruguay and Venezuela). The most common form of PID was predominantly antibody deficiency (53,2%), other well-defined PID syndromes such ataxia telangiectasia, Hyper IgE and Di George (22,6%), Combined T- and B-cell Immunodeficiency (9,5%), phagocytic disorders (8,6%), diseases of immune dysregulation (3,3%) and complement deficiencies (2,8%). All countries that participated in the first publication in 1998 reported increase in PID register cases, ranging between 10 and 80% (Leiva *et al.*, 2007).

In second LAGID record, Argentina recorded 852 cases of predominantly antibody deficiency, and Brazil 404 with predominates isothype deficiencies of light chain with normal numbers of B cells. Brazil reported 75 cases of Combined T-and B-cell Immunodeficiency and Argentina 69 cases. Like other well-defined syndromes, Argentina reported 60 cases of Di George Syndrome, 42 of Hyper IgE Syndrome and 40 of Wiskott-Aldrech Syndrome, Costa Rica 82 cases of DNA repair defects and Brazil 37 cases of Chronic

Mucocutaneous Candidiasis. Representing diseases of immune dysregulation, Argentina reported 22 cases of Immunodeficiency with Hypopigmentation, followed by 14 cases of Brazil. Congenital defects of phagocytic number, function or both, Brazil reported 50 cases of cyclic neutropenia and 42 cases of Chronic Granulomatous Disease (CGD), and Argentina 46 cases. Brazil reported 50 cases of deficiency complement, followed by 13 reports of Argentina (Leiva *et al.,* 2007). Like others studies, predominantly antibody deficiency was the principal PID observed in Latin America, Australia (Baumgart *et al.,* 1997; Kirkpatrick et al., 2007), China (Zhao *et al.,* 2006; Wang *et al.,* 2011), Egypt (Reda *et al.,* 2009), French (CEREDIH, 2010), Hong Kong (Lam *et al.,* 2005), Iran (Aghamohammadi *et al.,* 2002; Farhoudi *et al.,* 2005; Rezaei *et al.,* 2006), Italy (Luzi *et al.,* 1983), Kuwait (Al-Herz, 2008), Netherland (Zegers *et al.,* 1994), Norway (Stray-Pedersen *et al.,* 2000), Poland (Bernatowska *et al.,* 1998), Republic of Ireland (Abuzakouk *et al.,* 2005), Spain (Matamoros *et al.,* 1997; Milá *et al.,* 2001), Swiss (Ryser *et al.,* 1998), Taiwan (Lee *et al.,* 2011), Thailand (Benjasupattananan *et al.,* 2009), Tunisia (Bejaoui *et al.,* 1997) and USA (Javier *et al.,* 2000; Stiehm, 2007), Studies in other countries reveled major number of granulocyte dysfunction in India (Verma *et al.,* 2008), and Combined T-and B-cell Immunodeficiency in Turk (Shabestari *et al.,* 2007).

On October 14, 2009, a group of experts from six Latin American countries (Argentina, Brazil, Chile, Colombia, Honduras and Mexico) and representatives of LASID meet in Cartagena de Indias in Colombia to discuss particular needs of each country about PID. Also this year, was created on-line Program Registration in Latin America (Registration of Society for Immunodeficiencies Latin American-LASID) in site http://deficiencia.unicamp.br:8080/, to provide information of PID epidemiology in Latin America. This meeting was held on 28 and 29 April in São Paulo, with the participation of 90 participants from Argentina, Brazil, Chile, Colombia, Honduras and Mexico, three faculty members from the USA and a faculty member of ESID. The online registration for Latin America was adapted from the record set ESID in Europe; Latin America is supported by Jeffrey Modell Foundation and National Council for Scientific and Technological Development (CNPq) of Brazil. From this date, 24 centers were enrolled in diagnosis, treatment and research, with more than 600 registered patients. In others countries, the online database network make good results in records of PID (Eades-Perner *et al.,* 2007; Guzman *et al.,*; 2007; Gathmann *et al.,* 2009),

The LAGID has published four reports and proceedings; the first two papers focused on the prevalence and characteristics of PID patients in Latin America (Zelazco *et al.,* 1998; Leiva *et al.,* 2007); the third and fourth summarized deficiencies in PID diagnosis and treatment in Latin America and described features of educational outreach program, immunology fellowship program, and laboratory network aimed at correcting these deficiencies (Condino-Neto *et al.,* 2011; Leiva *et al.,* 2011). From July 2009 to September 2010, the LAGID recorded 838 cases of PID.

In April 2011, the registry of Immunodeficiencies completed two years, with more than 1000 cases reported from 35 centers representing various Latin America countries. Recently, the Committee decided to hold LASID collaborative studies with the recorded data to better understand profile of prevalent PID, such XLA, HIgM, and CGD, filling out form and sending data to protocololasidxla@bragid.org.br or protocololasidhim@bragid.org.br or protocololasiddgc@bragid.org.br depending on PID. The group also offers financial education programs in PID, with projects submitted to e-mail info@imunopediatria.org.br.

Those studies contributed with new insights on clinical presentation and impacted positively on the molecular diagnosis of PID. All together the Latin American experience shows that BCG complications is prevalent among SCID, T-cell deficiencies, and CGD patients; that fungal infections is highly prevalent among X-linked HIGM patients, and that ataxia-teleangiectasia is especially frequent in Mexico and Costa Rica. Currently Chile is building a new diagnostic center at University La Frontera that will interact with research centers in Argentina, Brazil, and Colombia. This strategy will strength even more the interaction among the several Latin American research centers.

Studies by LAGID showed numerous factors responsible for delay in diagnosis and treatment of patients with PID. Most pediatricians and family physicians in Latin America are not sufficiently trained to carry out the diagnosis of PID, there is a low amount of specialized installations for specific immunological tests, there is limited coverage for screening tests given by the government or private institutions, regional variability access to health and failure to comply with guidelines in certain countries and regions. To improve some of these aspects, diagnosis and treatment of patients with PID, experts from Latin America and the USA meet to discuss three specific programs, educational program (The L-Project), scholarships program and establishing of laboratory network to expand access to data (The Latin América Advisory Board on Primary Immunodeficiencies) (Leiva *et al.,* 2011; Condino-Neto *et al.,* 2011).

3.1 Educational program

The educational program (L-Project) was established to create increased awareness of general public, continuing education network on PID, promote basic and clinical research of PID and inform government officials in impact of PID on health published in Latin America. This program covers students, residents, pediatricians, nurses and officials involved in health system. It also emphasizes encouragement medical students seeking academic placement of teaching, research and clinical PID. These programs include summer school, containing cases and report on short-term programs associated with PID infection, dissemination of information by radio, television, websites, newspapers, magazines and educational material for community (Marodi & Casanova, 2009; Leiva *et al.,* 2011). This proposal directly contributes to knowledge generation and increase technological capacity of Latin America in this field. It is virtuous chain where all the researchers and the community involved propagate their knowledge acquired in other centers of reference, allowed expansion of existing lines of research in Brazil.

3.2 Summer school

Creating of Summer school is considered a viable solution to promote scientific interaction, and standardization of PID knowledge in different member countries because educational systems and medical residents differ in each country member (Condino-Neto *et al.,* 2011; Leiva *et al.,* 2011). In Brazil, São Paulo in 2006 was held the first Summer School, based on model proposed by ESID and CIS. This meeting was attended by 12 teachers of LAGID, ESID and CIS experts PID and 12 students, where they were focused biochemical and molecular diagnosis PID, major PID in Latin America; IVIG therapy guidelines, hematopoietic bone marrow transplantation; communication network LAGID. New meeting was held in 2008 in Temuco, Chile, and recently in 2010, Bahia, Brazil, with inclusion of 90 students from different Latin America countries.

3.3 Scholarship program offer

One of great difficulties encountered in developing countries for training professionals in PID is to awaken academic and professional interests, without compromising quality of life and survival of students and health professionals. Thus, different Latin American countries offer scholarships funded by educational institutions and other entities, governmental or private, with development of people involved and trained in specific areas of health. One of major problems seen in developing countries is the absence of jobs, which means that many students, just looking for graduate services that offer post-graduate scholarships, forgetting commitment they have with the community. Another problem in Latin America is formation of highly trained and qualified for certain areas of education and research, which are not absorbed by countries, end migrating to other parts of world. To resolve these problems, the Advisory Council LAGID determined availability of scholarships for doctors interested in area of clinical PID, as well doctors and teachers interested in immunology. The participating institutions were willing to participate in record LAGID, and grant applicants to submit personal statement, career development plan, and mentor involved with project statement of no conflict of financial interest and letters of recommendation. In this agreement, it was established that no country could be assigned more than two grants during period of two years, and beneficiaries of scholarship must publish report on its activities or clinical results or research (Leiva *et al.,* 2011).

3.4 Creation of centers of education, diagnosis and treatment

One of the major problems encountered in developing countries is lack of proper training of physicians and pediatric regional variability in access to educational program and establishment of diagnostic and treatment center. Thus, education and training are needed for specialists, pediatricians, general practitioners from different countries and regions of Latin America, ensuring that they are able to recognize warning PID signs. This includes creation of Summer School, symposia and conferences of PID. These educational efforts should also be understood to medical students, nurses and general public. For that, programs are needed government and private funding, and network (Leiva *et al.,* 2011). In Brazil, the Jeffrey Modell Foundation, and Baxter pharmaceutical industry, created on April 29, 2009 at Federal University of São Paulo-UNIFESP, the first Jeffrey Modell Diagnostic Center for PID in Latin America, based in field of Immunology pediatric UNIFESP, with working points in different parts of the country. The Jeffrey Modell Diagnostic Center operates in front of medical education, diagnosis and records of PID and patient education (Modell, 2007a; Modell, 2007b). Other diagnostic centers sponsored by the Jeffrey Modell will be opened in Mexico, Argentina, Colombia and Chile. Advancing educational model for educational outreach in Latin America is observed in the Brazilian Group of Human Immunodeficiency (BRAGID) (http://www.bragid.org.br), whose number of registered doctors increased from 190 in 2002 to 2.500 in 2009, after creation of local seminars on dating PID. The BRAGID provides information on warning PID, different clinical presentation PID of and diagnostic laboratories. Offer clinical cases that can be discussed in Internet. This model is followed in Colombia, which has specialized site that shows warning PID signs, types of PID and use of IVIG. In other Latin American countries, government agencies related to areas of health are more concerned with control of infectious diseases, and most professionals in the field of immunology work independently.

4. Conclusion

The PID are congenital and inherited diseases that affect the immune system, which occurrence in population varies by type of study and study group. Recent studies indicate that these values in the general population are underestimated and are one of the biggest problems and lack of knowledge, both worldwide and Latin America. Many factors compromise its knowledge, such as lack of education centers, professional structure, and laboratory records. The incidence of PID in Latin America is similar to that observed in different parts of the world, with predominantly antibody defects. In Latin America, adds to these, the lack of government support and private initiative. To redress this problem was created LAGID, which hosts Latin American countries concerned with knowledge of incidence, diagnosis, treatment and discovery of new PID. For this, congresses are held, online records and establishing laboratory training, diagnosis and treatment of PID, based on the model established in Europe.

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This book represents an overview on the diverse threads of epidemiological research, brings together the expertise and enthusiasm of an international panel of leading researchers to provide a state-of-the art overview of the field. Topics include the epidemiology of dermatomycoses and Candida spp. infections, the epidemiology molecular of methicillin-resistant Staphylococcus aureus (MRSA) isolated from humans and animals, the epidemiology of varied manifestations neuro-psychiatric, virology and epidemiology, epidemiology of wildlife tuberculosis, epidemiologic approaches to the study of microbial quality of milk and milk products, Cox proportional hazards model, epidemiology of lymphoid malignancy, epidemiology of primary immunodeficiency diseases and genetic epidemiology family-based. Written by experts from around the globe, this book is reading for clinicians, researchers and students, who intend to address these issues.

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