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Primary Immunodeficiency Diseases in Latin America: The Second Report of the LAGID[1] Registry

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This is the second report on the continuing efforts of LAGID to increase the recognition and registration of patients with primary immunodeficiency diseases in 12 Latin American countries: Argentina, Brazil, Chile, Colombia, Costa Rica, Honduras, Mexico, Panama, Paraguay, Peru, Uruguay, and Venezuela. This report reveals that from a total of 3321 patients registered, the most common form of primary immunodeficiency disease was predominantly antibody deficiency (53.2%) with IgA deficiency reported as the most frequent phenotype. This category was followed by 22.6% other well-defined ID syndromes, 9.5% combined T- and B-cell inmunodeficiency, 8.6% phagocytic disorders, 3.3% diseases of immune dysregulation, and 2.8% complement deficiencies. All countries that participated in the first publication in 1998 reported an increase in registered primary immunodeficiency cases, ranging between 10 and 80%. A comparison of the estimated minimal incidence of X-linked agammaglobulinemia, chronic granulomatous disease, and severe combined immunodeficiency between the first report and the present one shows an increase in the reporting of these diseases in all countries. In this report, the estimated minimal incidence of chronic granulomatous disease was between 0.72 and 1.26 cases per 100,000 births in Argentina, Chile, Costa Rica, and Uruguay and the incidence of severe combined immunodeficiency was 1.28 and 3.79 per 100,000 births in Chile and Costa Rica, respectively. However, these diseases are underreported in other participating countries. In addition to a better diagnosis of primary immunodeficiency diseases, more work on improving the registration of patients by each participating country and by countries that have not yet joined LAGID is still needed.

KEY WORDS: Primary immunodeficiency; Latin America; LAGID; Immunodeficiency epidemiology.

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INTRODUCTION

Although primary immunodeficiencies (PID) are rare inherited diseases, intense research studies in recent years have contributed to the understanding of the immunological defects and the genes involved in these disorders. Since the first case was reported in 1952, more than 100 types of PID are now known and their genetic defects have been identified (1). During the last decade, significant advances

have been made in the diagnosis and management of these conditions, which have improved their morbidity and mortality. However, epidemiological studies have shown wide geographical and racial variations in the prevalence and pattern of PID (2). Physicians and general practitioners are often not well informed about the clinical presentation of PID and as a consequence, patients die or remain untreated for several years.

Most developed countries have created registries to estimate the prevalence, incidence, and patterns of PID (3–11). However, epidemiological information of these diseases in developing countries is hampered by their limited resources to diagnose and treat these disorders. For this reason, in 1993, a group of immunologists from four Latin American Countries: Argentina, Brazil, Chile, and Colombia, formed the Latin American Group for Primary Immunodeficiency Diseases (LAGID). Important goals of this organization were to include other Latin American countries and to create registries of PID in each participating country. The first results of this effort were published by eight countries in 1998 (12).

After more than a decade since the creation of LAGID and its PID Registry, many of the objectives set forth by this group have been accomplished. The group has grown from the initial four to a total of 14 countries with a wide population range. Scientific meetings with case presentations and discussions with international guest speakers have been held annually. During these meetings, participating members have had the opportunity to report and discuss their registries. Educational programs and national scientific meetings with pediatricians have improved the early recognition and treatment of some of these diseases. Cooperation with scientists in countries with well-established immunology and molecular biology laboratories has helped other countries with limited resources, in the diagnosis of PID.

LAGID has also led to the development of patient and parent support groups and to the creation of a Web site and an online forum to keep members informed of important events and to discuss diagnosis and treatment options for patients with PID.

Here, we report on the impact of the continuing efforts of LAGID to increase the recognition and registration of PID patients in Latin America.

METHODS

Participating Countries

Countries participating in this report and their respective population and birth rate (13) are listed in Table I. Each country has one or two LAGID representatives, except for Brazil, which has three, who are responsible for coordinating, managing, and reporting the PID Registry to LAGID.

Data-Entry Form (Registry Questionnaire)

A two-page form initially designed in 1994 and adopted in 1995 was used to enter individual patient's basic demographic information. This form, which has been subsequently used to register all patients, includes: 1) the names of both the primary-care physician and the immunologist providing care; 2) patient's demographic information; 3) the PID diagnosis with clinical and phenotypic characteristics, molecular defect, mode of inheritance, associated diseases, secondary diseases, and malignancies; and 4) laboratory tests used for the diagnosis.

Table I. Population and Birth Rate of Countries Participating in PID Registry[a]

Country	Population in millions	1995–2000 Birth rate per 1000 population[b]	# Births per year 1995–2000	2000–2005 Birth rate per 1000 population[b]	# Births per year 2000–2005
Argentina	39.5	19.0	750,500	17.8	703,100
Brazil	186.1	20.7	3,852,270	18.0	3,349,800
Chile	16.0	18.7	299,200	16.5	264,000
Colombia	42.9	24.4	1,046,760	22.0	943,800
Costa Rica	4.0	22.3	89,200	19.8	79,200
Honduras	7.2	35.0	252,000	31.5	226,800
Mexico	106.2	24.6	2,612,520	22.3	2,368,260
Panama	3.1	24.6	76,260	22.4	69,440
Paraguay	6.3	32.4	204,120	30.5	192,150
Peru	27.9	25.6	714,240	22.1	616,590
Uruguay	3.4	17.3	58,820	15.2	51,680
Venezuela	25.4	23.4	594,360	20.2	513,080

[a]Source: International Database, U.S. Census Bureau, Washington, DC. Available at: http://www.census.gov.
[b]Birth rate average from each 5-year period.

Diagnostic Classification of PID

The criteria for the phenotypic diagnoses of PID were published in our first report (12) and it includes all diagnoses used by the World Health Organization (WHO) and the European Registry for Immunodeficiency Diseases (ESID) (14, 15). In this report, we have adopted the most recent classification developed by the International Union of Immunological Societies (IUIS) Primary Immunodeficiency Diseases Classification Committee (16). In this classification, the phenotypes are divided into eight categories: I. Combined T- and B-cell immunodeficiencies (ID); II. Predominantly antibody ID; III. Other well-defined ID syndromes; IV. Diseases of immune dysregulation; V. Congenital defects of phagocytic number, function, or both; VI. Defects in innate immunity; VII. Autoinflammatory disorders; and VIII. Complement deficiencies. The data justifying the diagnosis of each patient registered in each country was evaluated by the local LAGID representatives submitting the information for this report. The areas of each country that actively submitted patient data varied, so that some of the data reported in this registry may have a substantial reporting bias. The representatives of each LAGID country in this report are responsible for their own registry.

Estimation of the Minimal Incidence of PID Cases

The minimal incidence of PID cases in each country was estimated by calculating the average of cases per year reported in each period of the LAGID (estimated at 10 years for the first period and 8 years for the second period). Each average was divided by the country's birth rate for that period and the results were multiplied by 100,000. Information on each country's birth rate was obtained from the International Database, U.S. Census Bureau, Washington, DC (13).

RESULTS

A total of 3321 patients with PID have been registered in 12 Latin American countries (Table II). Since our first report in 1998 (12), the number of countries reporting their registries has increased from 8 to 12 with the addition of Honduras, Panama, Peru, and Venezuela.

The ID phenotypes in each major category are shown in Table II. The distribution of these categories and their phenotypes are: 1) 53.2% predominantly antibody ID; 2) 22.6% other well-defined ID syndromes; 3) 9.5% combined T- and B-cell ID; 4) 8.6% congenital defects of phagocytic number, function, or both; 4) 3.3% diseases of immune dysregulation; and 6) 2.8% complement deficiencies (Fig. 1).

Of the combined T- and B-cell deficiency phenotypes, severe combined immunodeficiency disease (SCID) was the most frequently reported. Selective IgA deficiency was the most common of the predominantly antibody deficiencies, with Argentina reporting the most cases. Within the other well-defined ID syndromes, ataxia telangiectasia was the most frequent deficiency, followed by hyper IgE syndrome and the Di George anomaly. The number of patients reported to have these two conditions varied widely from country to country. The variation in the number of ataxia telangiectasia patients was due to a large extent, to clusters in Costa Rica and in Mexico, with smaller numbers reported in the larger South American countries like Argentina and Brazil. By contrast, the largest numbers of the Di George syndrome patients were reported in Argentina and Chile with smaller numbers reported in other countries including the most populous one, Brazil. Chronic granulomatous disease was the most frequent among the phagocytic disorders and C1 inhibitor deficiency was the most common among the complement deficiencies (Table II).

The PID distribution reported by country is also shown in Table II. The country reporting the largest number of patients was Argentina, followed by Brazil and Mexico. Argentina and Brazil were the leading countries reporting the largest number of different phenotypes within each major category. In addition, Argentina reported seven cases that had molecular diagnosis: one case with IFNγ-receptor 1 deficiency, three cases with IL-12-receptor β chain deficiency, and three cases with ALPS (Table II).

A comparison between the first PID Registry reported in 1998 (12) by eight of these countries and the new cases reported here is shown in Fig. 2. The first period of approximately 10 years, includes all patients diagnosed prior to December 1996, and the second period includes patients registered from December 1996 to December 2004. All countries participating in the first report showed an increase ranging between 10 and 80% of PID patients reported. Uruguay, Mexico, and Argentina reported over a threefold increase in new PID cases, in comparison to the first report. In addition, Argentina has registered the highest number of cases in most major categories.

In order to evaluate the number of patients reported in relation to a country's susceptible population, we estimated the minimal incidence of XLA, CGD, and SCID. A comparison of the estimated minimal incidence between the two time-periods could only be performed for the eight countries that participated in the first report (12). Table III shows that the estimated minimal incidence of XLA, CGD, and SCID increased significantly from the

Table II. Number of Registered PID Cases by Phenotype and Country as of December 2004

Phenotype	Argentina	Brazil	Chile	Colombia	Costa Rica	Honduras	Mexico	Panama	Paraguay	Peru	Uruguay	Venezuela	Total
I. Combined T- and B-cell ID													
1–2. SCID	31	31	27	18	25	1	32	1	2		3	1	172
3. Omenn Syndrome								1					1
5. CD40 ligand deficiency	20	8	8	1	1	1	10		1	2	4		56
8. MHC class II deficiency					7								7
Other (with no molecular diagnosis)	18	36	6	9	1	2		7				1	80
Total	69	75	41	28	34	4	42	9	3	2	7	2	316
II. Predominantly Ab ID													
1. Severe reduction in all serum Ig with absent B cells	94	42	16	11	9	2	46	2	5	1	4	2	234
2. Severe reduction in at least two Ig isotypes with normal or low numbers of B cells	123	87	36	14	10	4	51	17	1	1	6	1	351
4. Isotype of light chain deficiencies with normal numbers of B cells	575	205	52	7	15	4	46	14	8	1	36	1	964
5. Specific antibody deficiency with normal Ig concentrations and numbers of B cells	21	35	12	2							4		74
6. Transient hypogammaglobulinemia of infancy	28	32	4	29	3	2			1		6	4	109
Other	11	3		4	11		2					1	32
Total	852	404	120	67	48	12	145	33	15	3	56	9	1, 764
III. Other well-defined ID syndromes													
1. Wiskott–Aldrech syndrome	40	18	10	5	8	5	21	1	1		1		110
2. DNA repair defects (other than those in I)	67	43	19	2	82		65	2	1	1	5	2	289
3. Thymic defects—Di George anomaly	60	4	25	3	1	2	18		1	1	1		116
6. Hyper-IgE syndrome	42	19	11	13		3	20	4	4	6	10	2	134
7. Chronic mucocutaneous candidiasis	14	37	9	6	2	6	10	1	1	1	3		90
Other	1	2	3				2	2				1	11
Total	224	123	77	29	93	16	136	10	8	9	20	5	750
IV. Diseases of immune dysregulation													
1. ID with hypopigmentation	22	14	11	5	5	1	9					3	70
3. X-linked lymhoproliferative syndrome (XLP)	1	1	3		3		2						10
4. Syndromes with autoimmunity	3												3
Other	10	11	3		1		3						28
Total	36	26	17	5	9	1	14	0	0	0	0	3	111

Table II. Continued

Phenotype	Argentina	Brazil	Chile	Colombia	Costa Rica	Honduras	Mexico	Panama	Paraguay	Peru	Uruguay	Venezuela	Total
V. Congenital defects of phagocytic number, function, or both													
4. Kostmann Syndrome	1	7		3			6						17
5. Cyclic neutropenia		50				3	18	2	7				80
7. Leukocyte adhesion deficiency type 1		2	1										3
8. Leukocyte adhesion deficiency type 2		7											7
15. Shwachman–Diamond syndrome	1												1
16–19. Chronic granulomatous disease (CGD)	46	42	18	7	8		31	1	4	1	3	1	162
20. Neutrophil G-6PD deficiency		1					1						2
21. IL-12 and IL-23 receptor β chain deficiency	3												3
23. IFG-γ receptor 1 deficiency	1												1
Other		3		2		1		2	2				10
Total	52	112	19	12	8	4	56	5	13	1	3	1	286
VI. Defects in innate immunity													
VII. Autoinflammatory disorders													
VIII. Complement deficiencies													
C4 deficiency	1	1					3	1					6
C2 deficiency	1	3					2					1	7
C3 deficiency		3					1			1	7		12
C5 deficiency		1											1
C1 inhibitor deficiency	10	28		4	1					1			44
Factor 1 deficiency		1									2		3
Other	1	13	5					1				1	21
Total	13	50	5	4	1	0	6	2	0	2	9	2	94
Total	1246	790	279	145	193	37	399	59	39	17	95	22	3, 321

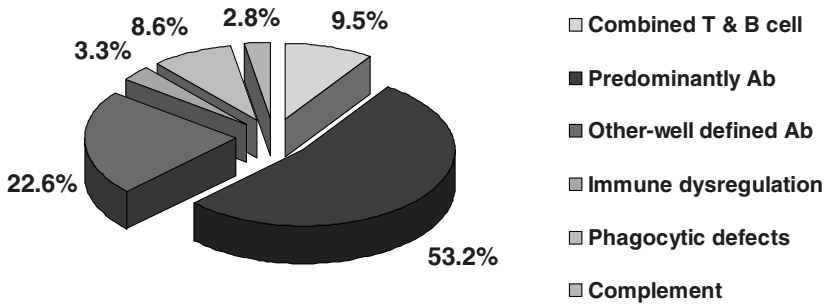

Fig. 1. Distribution of primary immunodeficiency diseases among 3321 patients in the LAGID Registry.

first to the present report, in all countries. In this report, the highest minimal incidence of CGD was 1.26/100,000 in Costa Rica, 0.85/100,000 in Chile, and 0.82/100,000 in Argentina, and that of SCID was 3.79/100,000 in Costa Rica and 1.28/100,000 in Chile.

DISCUSSION

Some of the goals set forth when LAGID was formed in 1994 have been accomplished and are reflected in this report. LAGID is now internationally recognized as a group of Latin American countries working together to improve the detection, diagnosis, and treatment of patients with PID who otherwise would have died or lived undiagnosed with a poor quality of life.

This report reveals that the most common form of PID was predominantly antibody deficiencies with IgA deficiency reported as the most frequent antibody disorder. This high frequency is also observed when the analysis is performed by country and is consistent with previous reports by Brazil, Argentina, and Colombia (17–19). This observation is similar to that reported not only in recent registries (9, 10, 20, 21) but also in PID registries reported as early as 1981 and 1983 by Japan and Italy, respectively (3, 4).

It remains to be determined if the elevated number of cases of MHC class II deficiency, ataxia telangiectasia and unclassified neutropenias in Costa Ricas is due to true clusters of diseases or to differences in diagnosing and reporting these conditions. The high number of patients with the Di George syndrome reported in Chile may be due to a specific research interest in this disease in that

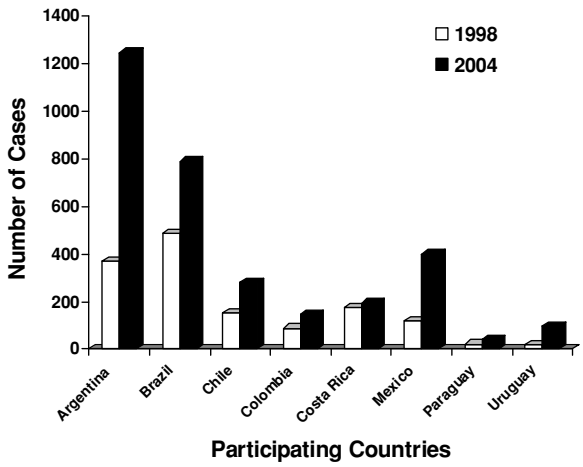

Fig. 2. Increase in PID Registry between1998 and 2004. Number of PID cases in countries that participated in the 1998 LAGID Registry report, and in this report.

Table III. Estimated Minimal Incidence of XLA, CGD, and SCID in 12 Latin American Countries

	Estimated minimal incidence (cases/100,000 births)[a]					
	XLA		CGD		SCID	
Country	1st Period	2nd Period	1st Period	2nd Period	1st Period	2nd Period
Argentina	0.61	1.68	0.15	0.82	0.08	0.55
Brazil	0.07	0.16	0.09	0.16	0.04	0.12
Chile	0.40	0.76	0.43	0.85	0.47	1.28
Colombia	0.08	0.15	0.05	0.09	0.06	0.24
Costa Rica	0.78	1.41	0.78	1.26	1.12	3.79
Honduras	N/A	0.11	N/A	0	N/A	0.05
Mexico	0.03	0.24	0.04	0.16	0.04	0.17
Panama	N/A	0.36	N/A	0.17	N/A	0.17
Paraguay	0	0.32	0.15	0.26	0.05	0.13
Peru	N/A	0.02	N/A	0.02	N/A	0
Uruguay	0.17	0.97	0	0.72	0	0.72
Venezuela	N/A	0.05	N/A	0.02	N/A	0.02

Note. N/A: Countries not participating in the first report.

[a]The minimal incidence of PID cases in each country was estimated by calculating the average of cases per year reported in each period (estimated at 10 years for the first period and 8 years for the second period). Each average was divided by the country's birth rate for that period (Table I) and the result was multiplied by 100,000.

country (22, 23), illustrating the importance of research interests in the detection of certain primary immunodeficiency syndromes. The same applies to the relatively significant number of CGD cases reported by Argentina, Brazil, Mexico, and Chile (24, 25) and XLA cases by Argentina (26).

The total number of patients diagnosed with PID does not reflect the actual prevalence of these diseases, as these numbers depend on the diagnostic capabilities present in each country and its regions and provinces, and on the willingness of physicians to report their cases to the LAGID registries. A registry maintained by the European Society for Immunodeficiencies (ESID) has collected data from 2631 patients from 36 documenting centers (15). Some countries have developed their own registry-based estimates of the frequency of PID in general, ranging from an estimated prevalence of 2.1/100,000 in Australia (8) to 6.8/100,000 in Norway (9). The identification and reporting of molecular diagnosis is still developing in Latin America, with Argentina having developed the largest capability of identifying various molecular abnormalities (26, 27).

Data from disease and mutation registries can be used to estimate the minimal incidence of a disorder, characterize epidemiologic features, and define a range of clinical characteristics in a patient population (2). However, current registries provide incomplete population-based data regarding the prevalence and incidence of PID. In 1992, the Immune Deficiency Foundation (IDF) initiated a registry of U.S. patients with CGD, and 5 years later expanded the project to include seven other disorders: hyper-IgM syndrome, XLA, CVID, WAS, SCID, LAD, and the DiGeorge syndrome (28). The most reliable data from these registries are for CGD, for which IDF has calculated a minimum estimated U.S. incidence of 1/200,000 live-born infants (28).

To determine if the LAGID Programs and Registry have contributed to increase the detection of new PID cases, we estimated the minimal incidence of three PID in the eight countries that participated in the previous report (12) and compared them to the current estimated incidence. Discrepancies between number of PID cases and population size are quite large. The low estimated incidence of XLA, CGD, and SCID in most Latin countries, compared to their minimal incidence in the U.S.A. (2, 29) and in some LAGID countries, reflects the need to improve the awareness of PID among pediatricians and the capability to detect and diagnose these diseases. However, the high incidence of these diseases, where the diagnosis is usually rather certain, also reveals that national efforts in some countries have led to a rate of detection of these diseases that is higher than in the United States.

Overall, the results shown in this report are encouraging and demonstrate an increase in the awareness and interest of pediatricians, internists, and general practitioners to improve the early diagnosis of PID patients in Latin American countries. Although some of the PID diagnoses can be accomplished with common routine laboratory tests, others require more sophisticated methodology that can be prohibitive for some developing countries. LAGID is developing a network of laboratories capable of diagnosing molecular abnormalities to help with this situation.

In addition to a better diagnosis of primary immunodeficiency diseases, more work on improving the LAGID Registry by each participating country and by countries that have not yet joined LAGID is still needed. This can be accomplished through educational and training programs, networking, and collaboration with well-established health care centers around the world, that have experience in the diagnosis and treatment of PID. In a collaborative effort with ESID, LAGID has now adopted the ESID electronic system for the registration of PID. The implementation of this electronic registry is presently in progress. Furthermore, it is in the process of converting the informal LAGID into a Society for Primary Immunodeficiencies that has the goal of extending the present LAGID activities to more regions of participating countries and to countries that still have not joined this effort.

APPENDIX

In addition to the authors, the following collaborators participated in this study. *Argentina*: Bozzola C, Garip E, Krasovec S, Miño O, Orellana J, Sierra de Criscuolo A, Gambarte L. *Brazil*: de Moraes Vasconcelos D, da Silva Duarte AJ. *Colombia*: Ortega MC. *Honduras*: Almendarez C. *Peru*: Vega H.

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