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Primary Immunodeficiency Diseases in Latin America: First Report from Eight Countries Participating in the LAGID[1]

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The Latin American Group for Primary Immunodeficiencies, formed in 1993, presently includes 12 countries. One goal was to study the frequency of primary immunodeficiencies in various regions of the American continent and to enhance knowledge about these diseases among primary-care physicians, as well as allergist–immunologists. Important for this purpose was the development of a registry of primary immunodeficiencies using a uniform questionnaire and computerized database. To date, eight countries have collected information on a total of 1428 patients. Predominantly antibody deficiencies were reported in 58% of patients, followed by cellular and antibody immunodeficiencies associated with other 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. The information gathered from this initial analysis of data will serve to expand the patient database to more areas within participating countries and to new countries and to increase collaboration toward better diagnosis and treatment of these diseases.

KEY WORDS: Primary immunodeficiencies; registry; Latin America.

INTRODUCTION

Knowledge about primary immunodeficiency diseases (PID) and their diagnosis and treatment is still fragmentary in many countries. Physicians and health-care authorities are often poorly informed about the clinical presentation, diagnosis, importance and health impact of these diseases. In response to this situation, clinical immunologists in several Latin American countries took the initiative in creating registries of PID. The results of these early efforts in Argentina, Brazil, Chile, and Colombia were presented and discussed at the III Congreso de la Asociacion Latinoamericana de Inmunologia in Santiago, Chile, in April 1993. These presentations were followed by an informal meeting and an agreement to coordinate efforts-in-progress with the following objectives: (a) to discover and compare the frequency of the different forms of PID in various regions of the American continent; (b) to document the incidence of these diseases in order to stress the importance of teaching clinical immunology in the medical curriculum; (c) to emphasize the importance of early recognition and treatment; (d) to develop diagnostic and treatment criteria for PID and to share information about diagnostic and treatment resources available in different areas of the continent; (e) to facilitate the development and coordinate the activities of patient and parent support groups; and (f) to promote research about PID, pooling resources and patient populations available for study across Latin America, and to invite other countries to share in this effort (1–4). Four years after the original decision to work together, the LAGID includes 12 countries, with several more announcing their interest in becoming active participants.

An important tool in the accomplishment of the goals set forth by the LAGID was the development of a PID registry using a uniform data-collection form and computerized database designed for the collection, management, and analysis of data on PID. Reporting PIDs detected in different countries has been important for

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Table I. Diagnostic Categories for the Registry Database (as They Appear on the Data-Collection Form)

Diagnoses
A. CLINICAL/PHENOTYPIC ID_____CLAS[a] # __ __
Age of diagnosis ____y ____m Time followed ____y ____m Lost to f/u ____y ____n
B. MOLECULAR/GENE DEFECT _____ CLAS # __ __
C. INHERITANCE. Sporadic __ XL__ Mat. carrier: ND__ Yes__ No__ Autosom reces__
(ND = not determined) dom__
D. ASSOCIATED DIS _____ CLAS # __ __
E. DIS 2nDARY to ID: No _____ Yes_____ #_____list_____ CLAS # __ __
F. MALIGNANCY_____ Age of onset: ____y____m

[a] The list of diagnoses with their corresponding classification numbers (CLAS #) is part of the registry data-collection forms and the computerized database.

increasing our knowledge of these diseases (5–10). Here we offer the first report of data on patients with PID from eight countries participating in the LAGID.

METHODS

Data-Collection Form (Registry Questionnaire)

A two-page form was developed to cover the patient's basic demographic information, the names of both the primary-care physician and the immunologist providing care, the diagnosis of the PID and other medical conditions, presentation, age and condition at the time of diagnosis, health impact, basic immunological testing and treatment, and follow-up information. Both the Spanish and the English versions of this form were designed so that shorter versions could be adapted for distribution to nonimmunologists.

Several parts of this form were specifically designed to test and subsequently enhance awareness of primary immunodeficiency disorders. These include questions about the age at onset of symptoms and the diagnosis of the immunodeficiency (Table I, English version), about patient diagnosis prior to becoming ill based on family history only, and also about patients whose diagnosis was established only by autopsy after death.

To develop the uniform data-collection form, questionnaires already in use in Argentina, Brazil, Chile, and Colombia, as well as Europe and Australia, were considered. A definitive format was adopted in April 1995 after a period of testing by interested physicians and societies in different countries. Patients diagnosed over the last 20 years were entered if accurate data were available.

PID Classification Lists

To accommodate the growing number of defined primary immunodeficiencies, as well as their gene and molecular defects, a diagnostic classification was developed which allows separate simultaneous identification of the immunologic phenotype, the mode of inheritance, the molecular defect, associated diseases, and also conditions secondary to the immunodeficiency (Table I). The phenotype diagnoses considered include all diagnoses used by the WHO (11) and the European Registry for Immunodeficiency Diseases (ESID). The criteria for each phenotypic diagnosis follow WHO recommendations. The minimum information necessary for entry into the registry identifies 1 of 67 PID phenotypes (12) supported by laboratory values recorded on the registry form (13). IgG subclass deficiencies were diagnosed based on normal values available in countries capable of performing IgG subclass determinations. For the diagnosis of hyper-IgE syndrome, evidence of recurrent boils, deep-seated infections, and/or chronic peridontitis was required, in addition to an elevated IgE level. Only phenotype diagnoses are included in this first report.

Database Program

A computer database program was developed using the Epi-Info Version 6.03 program distributed by the Centers for Disease Control and Prevention and sent on diskettes to all LAGID participants. This registry program allows data entry of all information recorded by the responding physician on the printed questionnaire and also allows direct statistical analysis of the data. In addition, data entered into the Epi-Info registry database can be uploaded to a mainframe computer for analysis with more powerful statistical packages. The use of this database program allows great versatility, as new items or questions of regional interest can be added without altering the basic structure of the program. It also allows the possibility of comparing the registries of different countries participating in the LAGID.

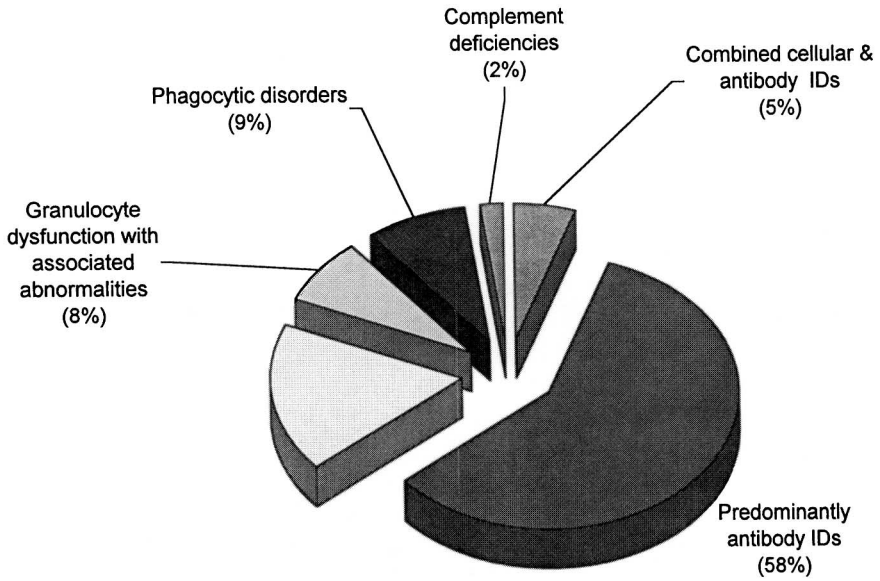

Fig. 1. Distribution of primary immunodeficiencies among 1428 patients reported in eight Latin American countries.

RESULTS

The eight participating countries reported a total of 1428 patients with PID. The registry questionnaires were completed almost exclusively by the immunologists involved in the care of the reported patients. Predominantly antibody deficiencies were most commonly reported (58%), followed by cellular and antibody immunodeficiency syndromes associated with other abnormalities (18%), immunodeficiency syndromes associated with granulocyte dysfunction (8%), phagocytic disorders (9%), combined cellular and antibody immunodeficiencies (5%), and complement deficiencies (2%) (Fig. 1).

The reported phenotypes in each major category are given in Table II. Within the combined cellular and antibody immunodeficiencies, severe combined immunodeficiencies (SCID) were by far the most frequent. IgA deficiency was the most frequently reported predominantly antibody deficiency, followed by common variable immunodeficiency (CVI) and X-linked agammaglobulinemia (X-LA). Among the cellular and antibody immunodeficiency syndromes associated with other abnormalities, ataxia telangiectasia was diagnosed most often, followed by chronic mucocutaneous candidiasis, Wiskott–Aldrich syndrome, and the DiGeorge anomaly. Two diagnoses accounted for the vast majority of immunodeficiency syndromes associated with granulocyte dysfunction: hyper-IgE syndrome and Chediak–Higashi syndrome. Chronic granulomatous disease was predominant among defects of phagocytosis, and C1 esterase inhibitor deficiency was the most frequent complement deficiency reported.

A breakdown of reported PIDs by country is also given in Table II. The largest number of patients was reported in Brazil, followed by Argentina and Costa Rica. The incidence of different PIDs shows important differences among participating countries. Notably, there is a high number of patients with ataxia telangiectasia in Costa Rica and Mexico. Both Brazil and Chile report the largest number of patients with chronic granulomatous disease, while Chile and Mexico report the largest number of patients with SCID. Only Brazil and Colombia report patients with specific antibody deficiencies with normal immunoglobulins.

DISCUSSION

The effort of creating a PID registry in Latin America, whose first results are reported here, have succeeded in bringing together the countries of this region and in identifying immunodeficiencies diagnosed in the participating countries. However, the total number of patients with the different PIDs reported here does not necessarily reflect the actual incidence or prevalence of these diseases. The time period for the collection of data was limited to the last 20 years, but in countries where this effort has just started, the time frame involved was much shorter. Furthermore, reporting from the different states, provinces, and regions within each country is still uneven. The four

Table II. Number of Registered Cases of PID by Phenotype and Country as of November 1996

Phenotype	Argentina	Brazil	Colombia	Costa Rica	Chile	Mexico	Paraguay	Uruguay	Total
1. Combined cellular and antibody immunodeficiencies									
SCID	6	17	6	10	14	11	1		65
Combined IDs		2			2				4
Cellular ID with normal Igs			1		2	2			5
Omenn syndrome						2			2
Reticular dysgenesis				1					1
Total									77
2. Predominantly antibody deficiencies									
IgA deficiency	134	174	18	35	21	15	5	11	413
CVI	52	46	13	8	26	5	1	3	154
X-LA	46	27	8	7	12	8		1	109
Transient hypogammaglobulinemia of infancy	17	31	5	3	2	1		1	60
IgG2 subclass deficiencies	20	9		4	5		1		39
Hyper-IgM syndrome	12	8	1	5	4	4			34
Antibody deficiency with normal Igs	1	15	3				1		20
IgG3 deficiency				2					2
IgG4 deficiency					2				2
IgG2 & IgA deficiency					1				1
IgG2 & IgG4 deficiency					1				1
Total									835
3. Cellular and antibody immunodeficiency syndromes associated with other abnormalities									
Ataxia telangiectasia	20	25	2	60	7	34	1		149
Chronic mucocutaneous candidiasis	7	18	4	2	7	8	2		48
Wiskott–Aldrich syndrome	12	4	4	7	4	3			34
DiGeorge anomaly	2	2	4	1	5	2	2		18
X-LP		1		3	1	1			6
Nijmegen syndrome	1								1
Total									256
4. Immunodeficiency syndromes associated with granulocyte dysfunction									
Hyper-IgE	14	10	10	14	14			1	63
Chediak–Higashi syndrome	11	15	1	4	7	5			43
LADI		3							3
Asplenia				1					1
Total									110
5. Phagocytic disorders									
Chronic granulomatous disease	11	36	5	7	13	10	3		85
Kostmann's disease		9				5			14
Cyclic neutropenia		4			2		5		11
G6-PD deficiency		7				1			8
Autoimmune neutropenia		3							3
Schwachman syndrome						1			1
Total									122
6. Complement deficiencies									
C1 inhibitor deficiency		8	2					2	12
C3 deficiency		3			1				4
C4 deficiency		3							3
Factor I (C3 inhibitor) deficiency	3	2							5
Properdin deficiency		2							2
C2 deficiency		1							1
C6 deficiency		1							1
Total									28
Total	369	486	87	174	153	118	22	19	1428

countries which were the first to initiate this effort in South America, i.e., Argentina, Brazil, Chile, and Colombia, and Costa Rica in Central America, where a different registry had been initiated independently of the South American effort, report the largest numbers of patients. Mexico, with the second-largest population of the eight countries, has just begun to collect data, so the number of reported patients is small. A detailed report of 166 Brazilian patients, included in this general report, has been published separately (14).

This initial report will contribute to the effort of increasing the number of participating countries and immunologists within each country in the future. Furthermore, as the same databases are expanded, it will be possible to describe the incidence of different PIDs over defined periods of time.

The frequency of ataxia telangiectasia, whose diagnosis does not require sophisticated laboratory methods, is probably a true reflection of higher gene frequencies for this abnormality in some populations. The diagnosis of other disease entities clearly reflect regional diagnostic capabilities, including the diagnosis of granulocyte disorders in Brazil, Chile, Colombia, and Mexico and the capability of determining specific antibodies to proteins and polysaccharides in Brazil and Colombia. The data collected here have been important to LAGID's efforts to offer training in frequently used diagnostic methods to different countries and to establish a network of laboratories willing to accept samples for more elaborate studies which are unlikely to be available in every country.

Several reports on registered cases of the various primary immunodeficiency syndromes agree in estimating that antibody deficiencies as a group are by far the most frequent ones (5–7, 9, 10). IgA-deficient patients included in this report are those who came to medical attention because of recurrent infections. A frequency of IgA deficiency of 1 in 965 blood bank donors had been reported earlier in Brazil (15). The reported frequency of antibody deficiencies and combined immunodeficiencies with a clear indication for IgG replacement therapy is already being used to help national health-care authorities plan the acquisition of IVIG for the treatment of these patients (Cornejo M, personal communication). This use of the data stresses the importance of continuing to collect patient information in order to make accurate estimates of IVIG needs.

The rather large collective numbers of patients in several important diagnostic categories shows how this registry may also serve as an instrument to identify patients and families for detailed analyses of the clinical presentation, diagnosis, treatment, and prognosis. LAGID will now encourage joint reports on specific disease entities. Furthermore, LAGID is now encouraging advanced studies of the molecular biology of various primary immunodeficiency syndromes, for which collaboration with immunologists in the recently formed Pan American Group for Primary Immunodeficiency (PAGID), the ESID, and other organizations is sought.

The LAGID registry is also an important instrument for education of physicians and health-care authorities. As such, its primary purpose is to inform them about the incidence of PID, the need for early diagnosis, updated diagnostic criteria, and the availability of treatment alternatives for patients suffering from these disorders. LAGID members are participating in each of the working groups recently established by PAGID to define diagnostic criteria for different primary immunodeficiencies. The consensus statements elaborated by these working groups will be translated and distributed to all LAGID members through publication in the *Boletín LAGID*. Furthermore, by the distribution of registry forms with the corresponding PID classification lists to pediatricians, internists, and general practitioners, the LAGID is calling the attention of responding primary-care physicians to the heterogeneity of PID, the rapid progress in the identification of the molecular basis of these diseases, the possibility of finding immunodeficiency diseases associated with many conditions not commonly known to have this association, and the devastating diseases which can occur secondarily to a PID.

APPENDIX

In addition to the authors, the following collaborators from each country participated in this study. *Argentina*: R. Craviotto, G. Feldman, V. Giraudi, A. Malbrán, M. Oleastro, N. Perez, M. E. Rivas, and M. Zelazko, Subcommittee on PID, Argentinian Pediatric Society—L. Bezrodnik and C. Baresse, H. de Niños Ricardo Gutierrez; C. Riganti and C. Cantisano, H. de Niños Pedro Elizalde; S. Rosenzweig, H. de Niños Juan P. Garrahan; D. Liberatore, H. Italiano (Buenos Aires)—C. Centeno, H. de Niños (Cordoba)—M. Maxit, H. de la Comunidad (Mar del Plata)—A. Gallardo, H. de Niños H. Notti (Mendoza)—R. Clays, H. Centenario (Rosario). *Brazil*: A. Zuliani, Faculdade de Medicina de Botucatu (Botucatu)—A. Condino-Neto, Faculdade de Pediatria, Universidade de Campinas (Campinas)—N. A. Rosário, Universidade Federal do Paraná (Curitiba)—E. Sarinho, Universidade Federal de Pernambuco (Recife)—E. Toledo, Faculdade de Medicina de São José do Rio Preto (São José do Rio Preto)—C. K. Naspitz, D. Solé, B. T. Costa-Carvalho, M. C. V. Rizzo, V. Nudelman, and I. Douglas, Escola Paulista de Medicina, Universidade Federal de São Paulo; A. S. Grumach, A. C. Pastorino, C. M. A. Jacob, and C. L. Diogo, Unidade de Alergia e Imunologia, Faculdade de Medicina; A. J. S. Duarte, Unidade de Alergia e Imunopatologia, Faculdade de Medicina Clinica, Universidade de São Paulo; R. Bellinati-Pires, Instituto Adolfo Lutz (São Paulo). *Chile*: B. Gonzáles, A. King, and G. Boldrini, H. Luis Calvo

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