Survival of pediatric patients with primary immunodeficiencies in a public hospital in Western Mexico

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ABSTRACT

A case series of primary immunodeficiencies is presented and outcome measures associated with survival among patients ≤ 16 years old are described. Diagnoses were made based on the criteria by the International Union of Immunological Societies. Survival was analyzed using Kaplan-Meier curves. Between 2004 and 2019, 40 patients were diagnosed with primary immunodeficiencies. The most common were immunodeficiencies affecting humoral and cell-mediated immunity (32.5 %) and predominantly antibody deficiencies (32.5 %). The median age at the onset of symptoms and at the time of diagnosis was 3.01 and 10.4 months, respectively. Thirty-five percent of patients died, and the risk was higher among those with immunodeficiencies affecting humoral and cell-mediated immunity and those who developed clinical manifestations and were diagnosed in the first 6 months of life.

Key words: *primary immunodeficiency diseases, severe combined immunodeficiency, primary antibody deficiency, immune system, immune system diseases.*

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INTRODUCTION

Primary immunodeficiency diseases (PIDs) are inherent defects in innate and adaptive immunity expressed as frequent and/or severe infections, autoimmune symptoms, lymphoproliferation, allergy, and cancer.[1-4] There is no information about the worldwide prevalence of PIDs. In Latin America, it has been estimated that the prevalence is 1 event/516 000 inhabitants, but, most likely, it is under-diagnosed.[5] In Mexico, in recent decades, the number of reported cases has trebled.[6]

In spite of the information available about PIDs, late diagnosis is common. The objective of this study was to describe a case series of PIDs among pediatric patients and the outcome measures associated with survival.

MATERIAL AND METHODS

This was an observational, retrospective study conducted at Hospital Civil de Guadalajara "Dr. Juan I. Menchaca" (HCGJIM) in the city of Guadalajara, Jalisco, Mexico. HCGJIM provides health services to an open, low-resource population.

The study included patients ≤ 16 years old who were diagnosed with PID at HCGJIM between January 1st, 2004 and December 31st, 2019. Patients with secondary immunodeficiencies were not included.

Diagnoses and PID classification were made based on the criteria proposed by the International Union of Immunological Societies.[7,8] The information about outcome measures was obtained from medical records (age at the onset of symptoms and at the time of diagnosis, family and hospitalization history, clinical manifestations, sex, type of PID, treatment, and deaths).

The "delay in diagnosis" was defined as the time elapsed between the onset of symptoms and diagnosis, and the "length of survival" was defined as the time elapsed between the diagnosis of PID and death or until the time of recording information for this study among live patients. Early deaths were those occurring in the first year of life. Parents were considered consanguineous

if they were biologically related as second cousins or closer.

Statistical analysis

For qualitative outcome measures, frequencies and percentages were estimated; whereas for quantitative outcome measures, median, minimum, and maximum were estimated. To test the hypothesis, the χ^2 test was done to compare proportions and the Mann-Whitney U test, to compare median values. Survival was analyzed using Kaplan-Meier curves with a log rank test to test the hypothesis. The IBM SPSS Statistics software, version 20, was used. The project was approved by the Ethics and Research Committees of HCGJIM under registry no. 0372/20 HCGJIM2020.

RESULTS

During the study period, 40 patients were diagnosed with PID; their median age was 10.4 months (maximum: 194.6, minimum: 1). Also, 75 % (n: 30) were males. Identified PIDs are shown in *Table 1*.

TABLE 1. *Primary immunodeficiencies diagnosed during the study period*

	n, %	Diagnostic method
Immunodeficiencies affecting humoral and cell-mediated immunity	**13 (32.5)**	
Severe combined immunodeficiency	10	Severe lymphopenia, (T-, B+/-, and NK+/-). Low levels of immunoglobulins, associated with opportunistic infections. Genetic defect confirmed in 3 (*RAG1*, *RAG2*, and IL2RG)
Hyper-IgM syndrome	2	T+ cells, B+ cells, high IgM levels, IgG, IgA, and IgE levels below normal for age. Opportunistic infections (miliary tuberculosis and cholangitis); 1 with CD40L deficiency and 1 with CD40 deficiency.
CD4 deficiency	1	T cell (CD3) levels below normal, at the expense of CD4 T cells (low). Normal B and NK cells. Normal serum immunoglobulins. Opportunistic infections (chronic suppurative BCG lymphadenitis and recurrent candidiasis).
Predominantly antibody deficiencies	**13 (32.5)**	
X-linked agammaglobulinemia	11	Very low or absent B cells. Low serum immunoglobulins. Recurrent bacterial infections (pneumonia, otitis, sinusitis, septic arthritis).
Common variable immunodeficiency	2	Hypogammaglobulinemia, recurrent infections, and autoimmunity (1/2).
Immunodeficiencies combined with syndromic characteristics	**8 (20)**	
Wiskott-Aldrich syndrome	7	Thrombocytopenia, eczema, low weight, chronic diarrhea. No WASp expression (3/7); the rest was diagnosed by association with an affected relative.
Ataxia-telangiectasia	1	Ataxia, ocular telangiectasia, pneumonia with lung abscesses.
Congenital defects of phagocyte number or function	**5 (12.5)**	
Severe congenital neutropenia	3	Skin abscesses, recurrent severe infections. Profound neutropenia (ANC < 100). ELANE mutation (1/3).
Glycogen storage disease	2	Neutropenia, hypoglycemia, hepatomegaly, hyperlipidemia.
Defects in innate and intrinsic immunity	**1 (2.5)**	
Mendelian susceptibility to mycobacterial diseases	1	Progressive, chronic suppurative *Mycobacterium bovis* and *Mycobacterium abscessus* lymphadenitis. IL-12Rβ1 mutation.
Total	**40**	

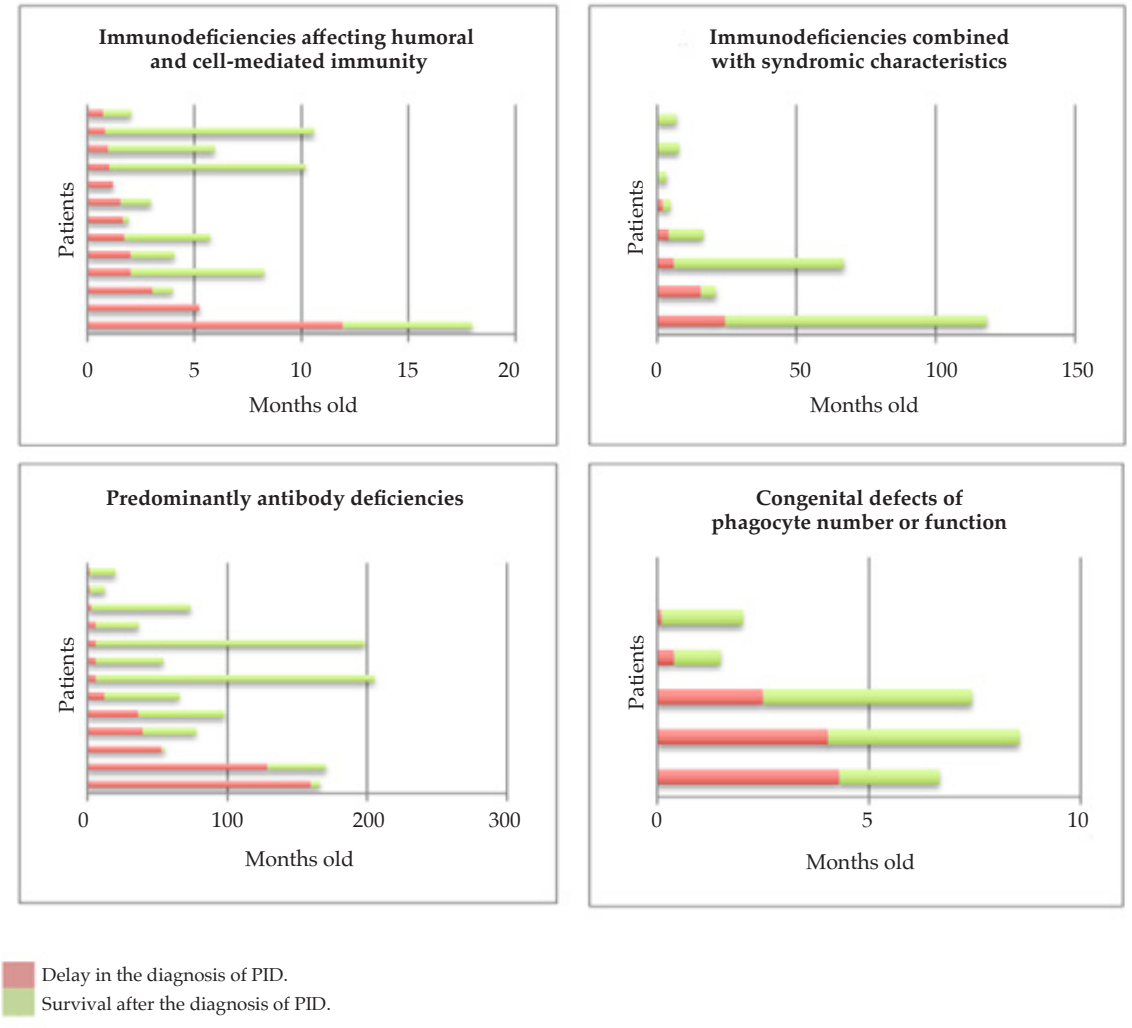
RAG: recombination-activating gene; IL2RG: interleukin 2 receptor subunit gamma; CD40L: CD40 ligand; BCG: Bacillus Calmette-Guerin; WASp: Wiskott-Aldrich syndrome protein; ANC: absolute neutrophil count; ELANE: elastase, neutrophil expressed; IL-12Rβ1: interleukin-12 receptor, beta 1.

A family history of PID was observed in 20/40; a history of early death among first-degree relatives, in 21/40; and consanguineous parents, in 3 cases. At the time of diagnosis, malnutrition was confirmed in 70 % (n: 28) together with atopic diseases in 32.5 % (n: 13); 3 patients had clinical data of autoimmunity (autoimmune hemolytic anemia in 2 and autoimmune thrombocytopenia in 1). During follow-up, 2 patients developed hematologic neoplasms (acute myeloid leukemia and primary lymphoma of the central nervous system).

Before the diagnosis of PID, 95 % (n: 38) had infections; 87.5 % (n: 35) corresponded to recurrent infections, and 63 % (n: 22) of these affected the upper and/or lower airways. Seven patients developed an adverse event to the Bacillus Calmette-Guerin (BCG) vaccine (3 disseminated infections and 4, local infections).

The median age at the onset of symptoms was 3.01 months (minimum: 0, maximum: 159.83). When comparing the age at the onset of symptoms based on the PID phenotype, it was observed that immunodeficiencies affecting humoral and cell-mediated immunity (IDHCI) had an earlier onset (median age: 1.67 months, minimum: 0.73, maximum: 11.9), compared to predominantly antibody deficiencies (PADs) (median age: 6.1 months, minimum: 1.57,

FIGURE 1. *Delay in diagnosis by primary immunodeficiency phenotype among pediatric patients of Hospital Civil "Dr. Juan I. Menchaca"*

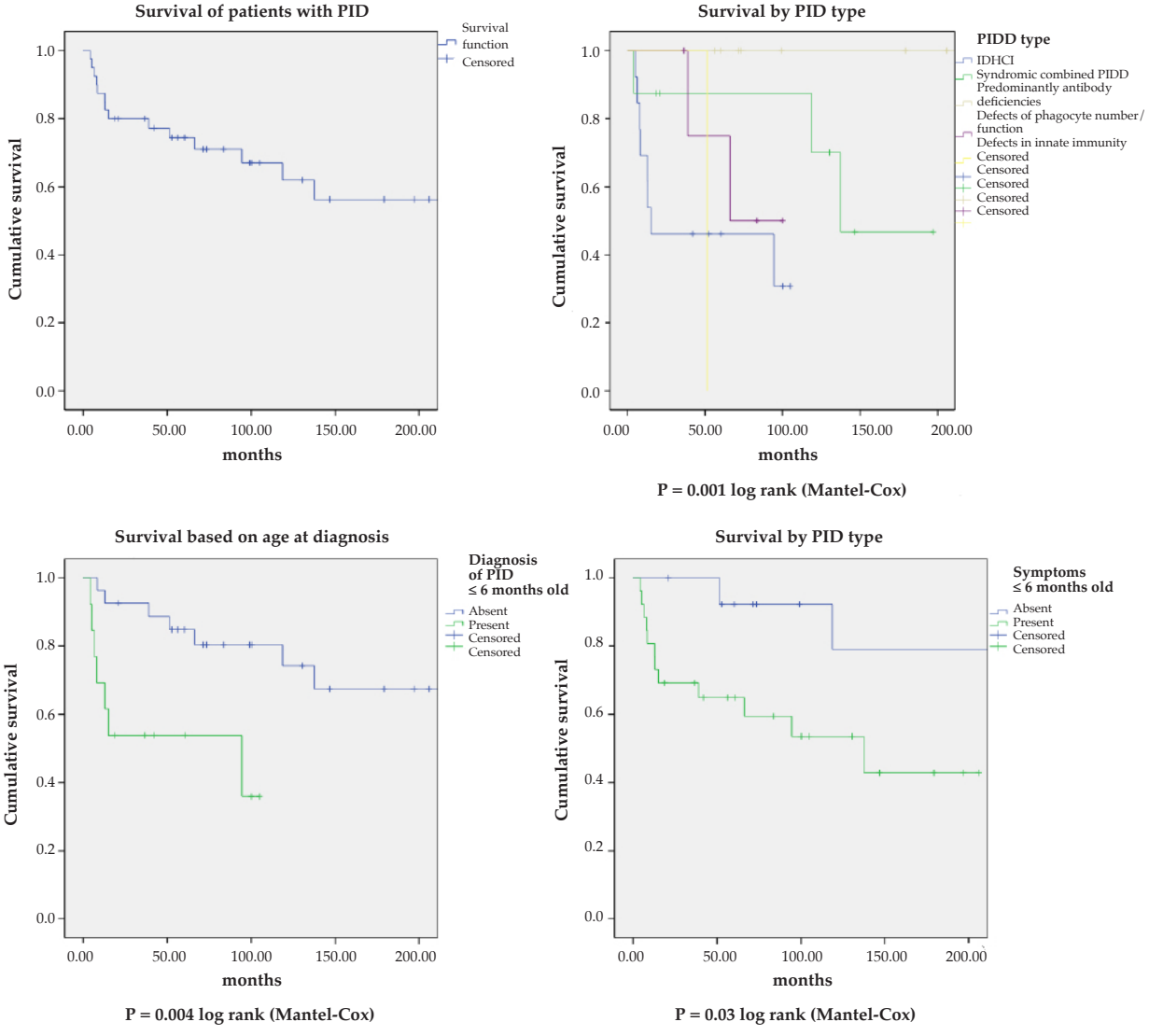


maximum: 159.83; $p < 0.001$).

The median delay in diagnosis was 6.3 months (minimum: 0, maximum: 199.4). Two patients were diagnosed at the time of the onset of symptoms because they had first-degree relatives with PID. In relation to the delay in the diagnosis by type of PID, it was observed that PADs were diagnosed with a longer delay (median: 41.6 months, minimum: 2.03, maximum: 199.4) compared to IDHCI (median: 2.0 months, minimum: 0.00, maximum: 9.7; *p*: 0.008) (*Figure 1*).

To the date of this study, 35 % of patients had died (n: 14). The cause of death was disseminated BCG-itis (3), pneumonia (3), sepsis (2), brain hemorrhage (1), lung abscess (1), abdominal abscess (1), meningoencephalitis (1), adenovirus infection (1), and graft-versus-host disease after bone marrow transplant (1). The remaining patients were receiving specific treatment for their PID phenotype: intravenous or subcutaneous immunoglobulins (13), granulocyte-colony stimulating factor (1), antibiotic prophylaxis (3),

FIGURE 2. *Survival curves of patients with primary immunodeficiencies*



PID: primary immunodeficiency disease; IDHCI: immunodeficiencies affecting humoral and cell-mediated immunity. Censored: patients receiving follow-up who had not died at the time of conducting the study.

in a protocol for bone marrow transplant (1), and under follow-up after bone marrow transplant (8).

Among patients with IDHCI, 10 had severe combined immunodeficiency (SCID). Of these, 8 underwent a bone marrow transplant; 4 survived; and 1 started the gene therapy protocol, but died due to adenovirus infection. Among children with Wiskott-Aldrich syndrome (WAS), 5 underwent a bone marrow transplant; 4 of them survived.

The analysis of mortality by type of immunodeficiency showed a higher mortality among patients with IDHCI (61.5 % versus 22.2 %, *p*: 0.038), whereas no death was reported among those with PAD (0 % versus 52 %, *p*: 0.001). *Figure 2* shows survival curves.

DISCUSSION

Patients with IDHCI and those with clinical manifestations or diagnosis of PID in the first 6 months of life showed a lower rate of survival. Infections were the leading cause of death.

Similar to our results, J. Wu et al. described a mortality rate of 38.4 % among 112 patients with PID. The average age at the onset of symptoms and at the time of diagnosis was 13 and 24 months, respectively. The prevalent PIDs were IDHCI (28.6 %) and, among patients with WAS and SCID, clinical manifestations were observed at a younger age: 1 and 4 months, respectively.

Mellouli et al.,[2] observed that, among patients with PID (n: 710), the average age at the onset of symptoms was 6 months and even younger among those with IDHCI (1.6 months) than those with PADs (90 months). Prevalent PIDs were IDHCI (28.6 %), and the overall mortality rate was 34.5 %, higher in the case of SCID (79 %).

In patients of HCGJIM with PID, the delay in diagnosis was 6.3 months and even longer among those with PADs. D. Gupta et al.,[10] reported an average delay in diagnosis of 5 years in 120 children with PIDs. However, comparing this indicator by PID type, they observed that the delay was 5 years for PADs and 3 months for in SCID. Late clinical manifestations among patients with PADs may be caused by the transplacental transfer of maternal antibodies and less severe infections compared to IDHCI.

Similar to what has been described in different articles,[9-12] 87.5 % of patients included in this series had recurrent infections, mainly affecting the airways, before the diagnosis of PID. Other clinical manifestations of PIDs are signs and symptoms caused by autoimmunity, allergies or malignancies.[11,13] This study identified 3 patients with autoimmunity and 2 who developed hematologic neoplasms. Lugo Reyes et al.,[11] described, in children with PID, non-infectious manifestations in 36 % of cases (allergies in 17 %, autoimmunity in 19 %, neoplasms in 2.4 %).

Medical records are an important tool to identify patients at a higher risk for PIDs. The family history is useful to justify, in some cases, the screening for PID before the onset of symptoms, while parental consanguinity increases the probability of developing autosomal recessive disorders.[2,10,14] An early diagnosis is relevant for PIDs. A timely treatment has been associated with better outcomes in terms of survival and adverse events caused by infections.[15]

The limitations of this study were the small number of patients and the retrospective information collection. However, the information observed here is useful to learn about the clinical behavior and course of some PIDs. ■

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