



Skin manifestations in pediatric patients with primary immunodeficiency diseases (PIDs) in a tertiary care hospital in Colombia

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ABSTRACT

Background: The current literature describes the characteristics of some skin manifestations in the context of primary immunodeficiency diseases (PIDs), also known as inborn errors of the immune system. However, there are hardly any data on the epidemiological trends of skin manifestations and PIDs in Latin America (LA). We aimed to describe the characteristics of patients with skin manifestations and the diagnosis of a PID treated at a tertiary hospital in Colombia.

Methods: This was a retrospective observational study. Data were taken from the institutional database of pediatric PIDs, which includes 306 patients under 18 years of age who attended a tertiary care center in Cali, Colombia for inpatient or outpatient services between December 2013 and December 2018. A trained third-year dermatology resident reviewed the electronic clinical records of all the patients in the database and double-checked patients who presented with cutaneous signs and symptoms.

Results: A total of 83 patients out of the original 306 patients (27.1%) presented with some type of cutaneous manifestation. Of these patients, 56.6% had atopic dermatitis, 56.6% reported at least one episode of skin infection, and some of the patients had both of these manifestations. Infections were more frequent in the PID group of combined immunodeficiency associated with well-defined syndromes and atopic dermatitis in the group of antibody deficiencies.

Conclusions: It is important to recognize dermatological clinical characteristics in patients with PIDs. More studies are necessary to establish recommendations regarding the approach of diagnosis and management of these patients.

Keywords: Primary immunodeficiency diseases, Inborn errors of immunity, Atopic dermatitis, Skin infection, Cutaneous manifestations

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INTRODUCTION

Primary immunodeficiency diseases (PIDs), also known as inborn errors of the immune system, are a heterogeneous group of inherited disorders caused by genetic mutations that alter the immune system.^{1,2} They include more than 300 genetic defects that predispose patients to autoimmunity, cancer, autoinflammation, immune dysregulation, allergic diseases, and recurrent, prolonged, atypical and/or severe infections.^{3,4}

The skin is an organ of great importance at the immunological level and is commonly affected in patients with PIDs.⁵⁻⁷ For this reason, dermatologists must bear in mind the cutaneous manifestations that are alarm signs possibly indicating *de novo* PID or, in other cases, when diagnosis is already present, the need to evaluate the progression of dermatological manifestations to offer suitable and timely treatment.⁵⁻⁷

Multiple articles have been published in the literature that link different skin manifestations in patients with PIDs, mainly recurrent skin infections and eczema; however, to our knowledge, there are hardly any data on the epidemiological trends of skin manifestations and PIDs in Latin America (LA).^{5,6,8} The objective of this study was to describe the clinical characteristics of the skin manifestations of pediatric patients treated at the PID clinic of a tertiary hospital in Colombia.

METHODS

This was a retrospective observational study. Data were taken from the institutional database of pediatric PIDs, which includes 306 patients under 18 years of age who attended our institution for inpatient or outpatient services between December 2013 and December 2018 with ICD-10 diagnosis codes D80-D89 registered in their electronic clinical records. Our institution is a tertiary care center that acts as a referral center for high complexity pathologies in southwestern Colombia. This database was completed by trained medical school students. Afterwards, a trained third-year dermatology resident reviewed the electronic clinical records of all the patients in the database and double-checked patients who presented with cutaneous signs and symptoms. A total of 83 patients of the original 306 patients

(27.1%) had skin manifestations and were included in this subanalysis.

The database includes a total of 109 variables, including sociodemographic, clinical, immunological, diagnosis, management, and different outcome variables. Some of the selected variables for this subanalysis were sex, family history of PID, family history of consanguinity, and diagnosis of PID based on the phenotypic International Union of Immunological Societies (IUIS) 2015 classification.⁹ Regarding cutaneous manifestations, the presence of atopic dermatitis (AD), prurigo, skin infections, chronic urticaria, seborrheic dermatitis, hair or nail alterations, pigment alterations, and vascular alterations were included in the database. A variable that further described the type of skin infection was included to discriminate viral, bacterial, parasitic, or fungal infections.

After completion of the database, an exploratory descriptive analysis was performed. Quantitative variables are expressed as medians and interquartile ranges (IQRs), while qualitative variables are expressed as proportions. The statistical software STATA© 12.1 was used for the analysis. The institution's Clinical Ethics Committee approved the study.

RESULTS

A total of 306 patients with a diagnosis of PID consulted our institution between December 2013 and December 2018. Of these, 21 patients were in the group of immunodeficiencies affecting cellular and humoral immunity, of which 8 patients presented with cutaneous manifestations. Twenty-three patients in the combined immunodeficiency group had associated or syndromic features, of which 9 patients presented with skin manifestations. A total of 229 patients were grouped into predominantly antibody deficiencies, and of these, 55 patients presented with cutaneous manifestations. In the group of congenital defects of phagocyte number, function, or both, there were 16 patients, of which 7 patients presented with skin manifestations. Three patients had defects in intrinsic and innate immunity, of whom 2 patients presented with skin manifestations. In the auto-inflammatory disorder group, a total of 7 patients had skin manifestations. There were 2 patients in

the complement deficiency group, and of these, 1 patient presented with cutaneous manifestations. A total of 83 patients (22.7%) had skin manifestations.

A total of 51 patients (61.4%) were male. Most of the patients were between 1 and 5 years of age (44.6%), 41% were older than 5 years of age, and 14.5% were younger than one year of age. The median age was 3.5 years (IQR 2-8 years). Eight patients (9.6%) had a family history of consanguinity, while only 1 patient had a family history of PID (Table 1).

The distribution of the diagnosis of PID in these patients, based on the IUIS 2015 classification, is presented in Fig. 1.⁹ The most common PID in patients with cutaneous manifestations was predominantly antibody deficiencies (66%), followed by immunodeficiencies affecting cellular and humoral immunity (11%).

The most common cutaneous manifestations in pediatric patients with PIDs were infections and AD, each present in 47 patients (56.6%) (Fig. 2).

In patients with predominantly antibody deficiencies, the most common cutaneous manifestations were AD in 63.6% and infections in 50.9% of the patients in this group of PIDs. Regarding infections in these patients, the most common

were pyodermitis in fourteen patients (25.5%) and superficial mycosis in 6 patients (10.9%). The only 2 patients with pigment alterations also had this PID diagnosis, 1 patient with nevus depigmentosus and 1 with segmental vitiligo (Table 2). It is worth mentioning that we had 5 patients with hyper-IgE syndrome and cutaneous manifestations. Three of these patients (60%) had AD, 1 with concomitant prurigo. Meanwhile, in the congenital defect in phagocytic number, function, or both groups, none of our patients reported skin granulomas or abscesses; however, they all reported localized disseminated Bacille Calmette-Guérin (BCG) infection (BCGosis).

The only vascular alteration in our cohort was purpura annularis telangiectodes of Majocchi in one patient with combined immunodeficiency with associated syndromic features. The patient had a molecular diagnosis of hyper-IgM syndrome with defective CD40 ligand production.

Thirty-six patients (43.4%) had no cutaneous infections. Table 3 discriminates the types of skin infections. The most common findings were pyodermitis in 21.7% of the patients and superficial mycosis in 18.1% of the patients. Viral manifestations were present in 12 patients. The most common viral infection was molluscum

	Total n=83 % (n)	<1 year n=12 % (n)	1-5 years n=37 % (n)	>5 years n=34 % (n)
Gender				
Female	38.6 (32)	58.3 (7)	35.1 (13)	35.3 (12)
Male	61.4 (51)	41.7 (5)	64.9 (24)	64.7 (22)
Family History of PID^{a,b}				
Yes	1.2 (1)	8.3 (1)	-	-
No	96.4 (80)	91.7 (11)	97.3 (36)	97.1 (33)
Family History of Consanguinity^{a,b}				
Yes	9.6 (8)	16.7 (2)	8.1 (3)	8.8 (3)
No	88.0 (73)	83.3 (10)	89.2 (33)	88.2 (30)

Table 1. Sociodemographic characteristics in patients with PIDS and cutaneous manifestations treated in a tertiary hospital in Colombia between 2013 and 2018 according to age group. a. Some missing values. b. Patient with family history of PID who also had consanguinity

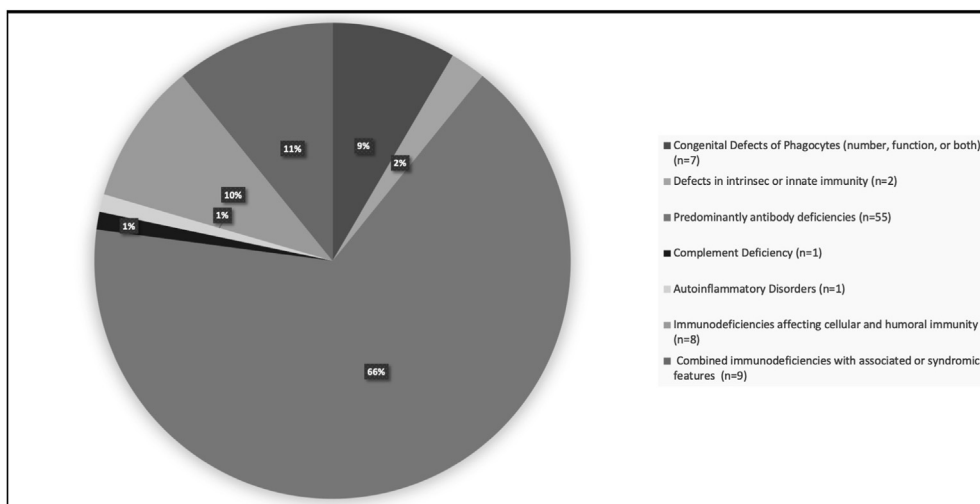


Fig. 1 Distribution of PID diagnosis according to IUIS classification in pediatric patients with PIDs and cutaneous manifestations treated in a tertiary hospital in Colombia between 2013 and 2018

contagiosum (6 patients), followed by other viral warts (4 patients) and herpes simplex (2 patients).

DISCUSSION

The estimated global prevalence of PIDs in the literature is 41.4–50.5 cases per 100,000 people in the general population.^{1,2,10} However, data vary depending on the geographical area studied, and different estimates have been reported—4.2 cases per 100,000 people in Switzerland, 30.5

cases per 100,000 people in Turkey, 24.9 cases per 100,000 people in Kuwait, and estimated prevalence of up to 50.5 per 100,000 people in the United States.^{11–14} In Colombia, there is underreporting of these data; however, the estimated prevalence is 2.07 cases per 100,000 inhabitants for 2020.⁸

The most common PID in patients with cutaneous manifestations was predominantly antibody deficiencies. This finding is similar to reports from other cities in Colombia, namely Bogotá (56%) and

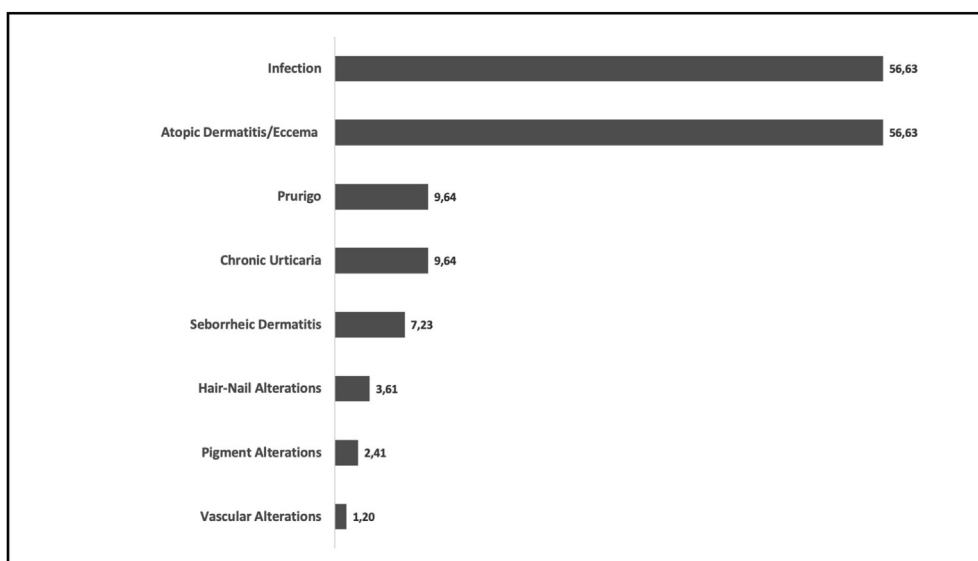


Fig. 2 Cutaneous Manifestations in Patients with PIDs treated in a tertiary hospital in Colombia between 2013 and 2018

	Immunodeficiencies affecting cellular and humoral immunity	Combined immunodeficiencies with associated or syndromic features	Predominantly antibody deficiencies	Congenital defects of phagocytes (number, function, or both)	Defects in intrinsic or innate immunity	Autoinflammatory disorders	Complement deficiency
	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Total	100.0 (8)	100.0 (9)	100.0 (55)	100.0 (7)	100.0 (2)	100.0 (1)	100.0 (1)
Atopic Dermatitis	50.0 (4)	55.6 (5)	63.6 (35)	42.9 (3)	-	-	-
Prurigo	25.0 (2)	22.2 (2)	21.8 (12)	28.6 (2)	-	-	-
Infection	62.5 (5)	66.7 (6)	50.9 (28)	71.4 (5)	100.0 (2)	100.0 (1)	-
Seborrheic Dermatitis	12.5 (1)	11.1 (1)	7.3 (4)	-	-	-	-
Chronic Urticaria	12.5 (1)	-	9.1 (5)	14.3 (1)	-	-	100.0 (1)
Hair and Nail Alterations	-	-	3.6 (2)	-	-	100.0 (1)	-
Pigment Alterations	-	-	3.6 (2)	-	-	-	-
Vascular Alterations	-	11.1 (1)	-	-	-	-	-

Table 2. Cutaneous manifestations in patients with PIDs according to IUIS classification treated in a tertiary hospital in Colombia between 2013 and 2018

	% (n)
Pyodermitis	21.7 (18)
Superficial Mycosis	18.1 (15)
Nonspecified Viral Wart	4.8 (4)
Only Molluscum Contagiosum	3.6 (3)
Pyodermitis and Molluscum Contagiosum	2.4 (2)
Herpes Simplex	2.4 (2)
Scabies	1.2 (1)
Pediculosis	1.2 (1)
Superficial Mycosis and Molluscum Contagiosum	1.2 (1)

Table 3. Presence of cutaneous infections in patients with PID diagnosis in a tertiary hospital in Colombia

(74.4%).^{15,16} We consider that this is because antibody deficiency is the most prevalent PID in our population, and this specific PID is associated with long-term cutaneous manifestations.^{2,3,13}

Dermatological manifestations are common in PIDs and have been reported in up to 48% of patients with any of these pathologies.^{5,6,17-19} In approximately 39% of cases, skin lesions are the first manifestation of PID.^{5,6,17,18} Our study showed a prevalence of 27.1% for skin lesions in patients with a diagnosis of PID, which is lower than that reported in the literature, possibly due to our small sample size and underdiagnosis of PID in our health system.^{17,18,20} It should be taken into account that the same patient can have more than 1 cutaneous manifestation at different times during their disease.^{5,6,17,18}

The prevalence of cutaneous infections and eczema was 56.6% for both. Al-Herz et al evidenced a prevalence of recurrent skin infections of 30% versus a prevalence of 19% of eczema in patients with PIDs.⁶

Skin infections are among the most common findings in patients with PIDs.⁶ In our population, we found 47 children (56.6%) with dermatological symptoms of infectious etiology—18 children (21.7%) had bacterial infections, 15 children (18.1%) had superficial mycoses, and 2 patients (2.4%) had skin infections such as pediculosis and/or scabies. Three patients (3.5%) had molluscum contagiosum, 2 patients (2.4%)

had herpes simplex, and 4 patients (4.8%) had viral warts. Very similar results were reported by Berron-Ruiz and colleagues in Mexico City.²⁶

Bacterial infections were the main cause of infection in our patients, followed by fungal infections and viral infections. Al-Herz and Nanda found similar prevalences in these 3 groups in patients with PIDs;⁶ however, in a report by Berron-Ruiz et al fungal infections were also more frequent than viral infections,²⁶ as we reported, possibly because these types of infections, as well as bacterial abscesses, are part of the original warning signs for the early detection of PIDs, as are environmental factors such as living in tropical climates that favor fungal infections.

In our population, 56.6% of patients corresponded to AD and other subtypes of moderate to severe grade with a history of multiple acute outbreaks, a percentage that is higher than the prevalence of AD in the general population and the reported prevalence of 22% for AD in PIDs.¹⁷⁻²⁷ We also observed that 18 patients (21.7%) had a diagnosis of chronic prurigo at some point during their follow-up, which could even be a clinical manifestation of AD, considering that approximately half of patients with atopy have chronic prurigo.²⁸

The literature reports that up to 7% of erythroderma cases in childhood are associated with a PID, including the associated syndromes Comél-Netherton syndrome and Omenn syndrome.²⁴ In

our study, only 1 patient presented with erythroderma, which was consistent with a diagnosis of Omenn syndrome. This patient underwent bone marrow transplantation, leaving a residual humoral deficit. In our population, only 3 patients (3.6%) had hair and nail alterations in the context of congenital dyskeratosis.

Additionally, children with PIDs are at increased risk for immune dysregulation and autoimmune conditions.⁷ Autoimmune dermatoses, such as vitiligo, with an estimated prevalence in the pediatric population between 0.5 and 2%, occur with a higher prevalence in patients with humoral immunodeficiencies, mainly common variable immunodeficiency (4.3%) and selective IgA deficiency (14.3%).^{5,29} We observed 2 patients with concomitant vitiligo associated with their PID (2.4%), which was lower than the rate reported in the literature, possibly due to the age of the study population and the sample size.^{5,26}

Most dermatological lesions in PIDs are not pathognomonic for a specific immunodeficiency and can be present even in patients with normal immunity, which is why the clinical approach of these patients with cutaneous involvement should be considered in the context of the natural history of their disease in the case in which there is an established diagnosis of PID. Not only should the dermatological diagnosis be taken into consideration; the degree of involvement, the response to other treatments, the evolution over time, the changes or heterogeneity of the lesions, and the prevalence established for this skin diagnosis in the population should also be compared.⁵⁻⁷

Limitations

Some of the limitations of this study, which are secondary to its retrospective nature, include the fact that the patients already had a diagnosis of PID; therefore, it is unknown how many had skin involvement as the first manifestation of their PID. Additionally, we included data from a five-year time period; during this time, awareness of these pathologies increased, which could mean that during the earlier years of the recollected data, the diagnosis of PID may have been missed.

CONCLUSIONS

This study shows the importance of recognizing dermatological clinical characteristics in patients with PIDs. This is the first study to be carried out in southwestern Colombia, which is why more research is necessary to establish recommendations on the approach to skin lesions in the pediatric population and to establish dermatological alarm signs to suspect PID when undiagnosed.

Abbreviations

PIDs-Primary Immunodeficiency Diseases; LA- Latin America; IUIS-International Union of Immunological Societies; AD-Atopic Dermatitis

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None.

Availability of data and materials

On institutional data base (BD Clinic), it is readily available to download. We can send you the file if it's necessary.

Ethics approval

#1241 from Institutional Ethics Committee.

Consent for publication

Approved by all authors.

Author contributions

WLQ: Conceptualization, methodology, data collection, manuscript writing original draft, manuscript final review and editing.

DC: Conceptualization, data analysis, manuscript writing original draft, manuscript final review and editing.

LTC: Conceptualization, methodology, data collection, data analysis, manuscript final review and editing.

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HP: Conceptualization, methodology, manuscript final review and editing.

AV: Conceptualization, methodology, manuscript final review and editing.

MO: Group leader, conceptualization, methodology, data collection, data analysis manuscript writing original draft, manuscript final review and editing.

Declaration of competing interest

None.

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