

Sensitization to Aeroallergens in Patients with Primary Immunodeficiencies

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Keywords

Primary immunodeficiencies · Allergy · Sensitization · Aeroallergens · Asthma · Rhinitis · Atopic dermatitis · Skin prick testing

Abstract

Background: Primary immunodeficiencies (PID) are a heterogeneous group of diseases that cause alterations in the immune system, leading to the increased susceptibility to infections, autoimmune diseases, and malignancies. The aim was to evaluate the presence of clinical manifestations and diagnoses of asthma, rhinitis, and atopic dermatitis in patients diagnosed with PID, and correlate these with allergen sensitization verified by skin prick testing (SPT). **Material and Methods:** This cross-sectional, descriptive, and observational study was conducted from February 2015 to February 2016. We performed a medical report analysis and SPT for aeroallergens in patients with a PID diagnosis. **Results:** Thirty-one patients with a PID diagnosis were included. The mean age of the participants was 15.41 years. From the 31 patients, 28 had symptoms suggestive of allergic disease (asthma, rhinitis, and atopic dermatitis) and only 7 presented positive SPT for at least 1 aeroallergen. **Conclusion:** The frequency of allergenic sensitization in the group of patients with PID and symptoms suggestive of asthma, rhinitis, or

atopic dermatitis is lower than that found in the general population, probably due the impairment of IgE formation secondary to their immunologic alterations.

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Introduction

Primary immunodeficiencies (PID) comprise a heterogeneous group, currently consisting of >320 diseases caused by genetic mutations that lead to alterations in the development and function of the immune system. These diseases are characterized by recurrent, severe infections and/or by unusual or low pathogenicity agent, autoimmune or inflammatory manifestations and a greater predisposition to neoplasia [1].

Although initially referred to as rare, the current prevalence of PID is unknown. Recent surveys conducted in more than 40 countries estimate that the frequency of these varies from 1/2,000 to 1/10,000 individuals [2]. Nevertheless, it is suspected that such numbers are underestimated, since cases of immunodeficiency can be underdiagnosed [3]. A 2007 study conducted in the USA

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concluded that the prevalence of all immunodeficiencies was approximately 1/800 to 1/2,000 individuals [3].

A previous study observed a high prevalence of respiratory and allergic diseases in patients with partial or total IgA deficiency; the majority (95%) of the patients had varying degrees of allergic rhinitis, with a high association with asthma (approx. 70%) as well as other autoimmune alterations [4, 5]. To note, immediate-reading skin prick testing (SPT) or measurements of specific IgE in serum are used as tools to verify allergic sensitization in the diagnosis of allergic diseases [6, 7].

Since PID involve different causes and immunological changes, the presence of allergen sensitization in this group of patients depends on the immunological defect present in each individual. In this context, the objective of this study was to evaluate the presence of the clinical manifestations and diagnosis of asthma, rhinitis, and atopic dermatitis in patients diagnosed with PID, and correlate these with allergen sensitization verified by SPT.

Material and Methods

This was a cross-sectional, descriptive, and observational study using nonprobability sampling with the convenience sampling method, performed at the Outpatient Clinic for Immunodeficiency of the Hospital de Clínicas of the Universidade Federal de Uberlândia (HC-UFU) from February 2015 to February 2016.

The patients with a PID diagnosis or their parents/guardians were recruited and informed about the study procedures that included SPT and a questionnaire on allergic diseases based on the International Study of Asthma and Allergies in Childhood (ISAAC) [8]. All patients were followed by senior allergy and/or pulmonologist physicians in the same institution, and, if necessary, their medical records were consulted for verification. Patients and guardians who agreed to participate in the study signed an informed consent form. The study was approved by the Research Ethics Committee of the UFU under the protocol No. 056239/2015.

SPT was performed with the following commercially acquired standard extracts of aeroallergens: *Dermatophagoides pteronyssinus* (Der p), *D. farinae* (Der f), dog epithelia (*Canis familiaris*), cat epithelia (*Felis domesticus*), cockroach (*Periplaneta americana*), *Blomia tropicalis* (Blo t), grasses, *Alternaria alternata*, *Aspergillus fumigatus*, *Cladosporium herbarum*, *Penicillium notatum*, histamine, and a negative control (Immunotech®, Rio de Janeiro, Brazil). The tests were performed according to the guidelines of the Brazilian Association of Allergy and Immunology (Associação Brasileira de Alergia e Imunologia, ASBAI) [7].

The questionnaire presented topics with the purpose of verifying the clinical diagnosis of allergic diseases including asthma, allergic rhinitis, and atopic dermatitis in the individual and their first-degree relatives, as well as lifestyle habits and housing conditions, age, and gender data.

Statistical analysis was performed using measures of central tendency and the Excel® program.

Table 1. Primary immunodeficiency (PID) diagnoses of study participants

Specific antibody deficiency	12
Common variable immunodeficiency	7
Agammaglobulinemia	1
Transient hypogammaglobulinemia of infancy	3
Hyper IgE syndrome	1
Wiskott-Aldrich syndrome	1
DiGeorge syndrome	1
Congenital neutropenia	1
Ectodermal dysplasia associated with PID	1
Selective IgA deficiency	1
DOCK8 deficiency	1
CD4 deficiency	1

Results

Thirty-one patients with a PID diagnosis were included. The mean age of the participants was 15.41 years (range 1–67 years); 64.52% ($n = 20$) were male and 35.48% ($n = 11$) were female. Mean age was 6.02 years (range 0–58 years) for the onset of typical PID symptoms (infections) and 12.23 years (range 0.1–61 years) for PID diagnosis, with a mean interval of 6.21 years between the onset of symptoms and PID diagnosis.

In this cohort of patients, 24 (77.42%) had predominantly antibody defects, 3 (9.68%) had genetic syndromes associated with immunodeficiencies, 3 (9.68%) had combined immunodeficiencies, and 1 (3.22%) had a defect in their innate immunity. Table 1 shows the PID diagnoses of the study participants.

At the time of data collection, 13 (41.94%) patients were receiving intravenous immunoglobulin replacement therapy monthly, 15 (48.39%) were on prophylactic antibiotics, and 1 (3.23%) was receiving filgrastim weekly.

Twenty-eight (90.32%) patients had symptoms suggestive of allergic diseases. Regarding asthma, 15 (48.30%) had a diagnosis suggestive of asthma, and 6 (40.00%) of them were on inhaled corticosteroids with or without slow-acting bronchodilators. In this group of patients, only 3 (20%) had positive SPT for aeroallergens. The diagnosis suggestive of rhinitis was observed in 13 (42.93%) patients, with positive SPT in 5 (38.40%) of these. Atopic dermatitis was diagnosed in 6 (19.30%) and SPT was positive in 3 (50%) patients.

Seven (22.58%) patients presented with positive SPT for at least 1 aeroallergens. Most patients with positive test were sensitized to more than one allergen, with 6 positive for Der p, 5 for Der f, 3 for Blo t, 1 for cat epithelia, and 1 for *P. notatum*.

Table 2. Correlation of the diagnosis of asthma, rhinitis, and dermatitis with sensitization to aeroallergens in 31 patients

Disease	Patients	Sensitization	Immunodeficiencies and sensitization
Asthma	15 (48.3)	3/15 (20.0)	DOCK8, SAD, congenital neutropenia
Rhinitis	13 (42.9)	5/13 (38.4)	SAD (3), CD4 deficiency, congenital neutropenia
Dermatitis	6 (19.3)	3/6 (50.0)	DOCK8, SAD, congenital neutropenia

Values in parentheses are percentages. SAD, specific antibody deficiency.

Table 2 correlates the diagnosis of asthma, rhinitis, and dermatitis with sensitization to aeroallergens, showing an asthma diagnosis in 15 (48.3%) of the patients in this cohort, rhinitis in 13 (42.9%), atopic dermatitis in 6 (19.3%), and the crescent ratio of sensitization in these diseases, respectively.

Discussion

PID are diseases requiring wide information to be spread among health professionals since they are underdiagnosed in many centers. [9]. In this study, the average time between the onset of PID symptoms and diagnosis was 6.21 years, shorter than that previously described in the literature, i.e., 12.5 years (in the last decade) [10, 11]. The presence of a reference unit in clinical immunology with regional coverage may have influenced the reduction of the average time to the diagnosis of PID.

Predominantly, antibody defects are found to be the most frequent, followed by genetic syndromes, combined defects, and phagocyte disorders [11, 12]. Allergic diseases and allergen sensitization in a group of patients with PID have previously only been reported in 2 studies. One of these, performed in Turkey, presented a particular situation where 32.39% of the cohort of PID patients had a diagnosis of IgA deficiency or IgG-subclass deficiency, both conditions that usually present fewer infections than other PID [13, 14]. This is a different profile of PID patients from that of our cohort, probably because our immunology clinic receives patients referred for recurrent infections, meaning the number of patients with an IgA or IgG-subclass deficiency is very low. Notwithstanding, the frequency of patients with PID sensitized to SPT in our setting was higher than what they observed [13].

The other study where PID patients were evaluated recruited only common-variable immunodeficiency (CVID), and verified the presence of allergen sensitiza-

tion in approximately 5.6% of the cases [14]. Allergen sensitization was observed in only 3.28% of the patients with CVID and an asthma diagnosis. This low frequency was confirmed in our study, since no patient with CVID had a positive SPT.

Allergic rhinitis was previously found in one-third of patients diagnosed with PID [13], i.e., lower than what we observed (42.93%). Meanwhile, the presence of reported atopic dermatitis in the same study was 25%, higher than in ours (19.3%). A study published in the same population area comparing PID patients with a regular population without PID [6], found that of 212 patients with a diagnosis of rhinitis and asthma 73.50% had SPT positivity, higher than what we described in PID patients. Both studies show the same sensitization profile, albeit to a lesser extent, corroborating the theory that sensitization to aeroallergens depends on an interrelationship between genetic susceptibility and exposure to allergens.

We speculate that the low rate of allergen sensitization in PID patients with allergic symptoms could be explained by the impairment of fully active effector cells (e.g., Th2) or molecules like cytokines and receptors; due to specific immune alterations, a complete IgE response fails to develop. On the other hand, the presence of allergen sensitization in a CD4-deficient patient in this cohort is worth noting. We believe that IL4/IL13 could be produced by innate cells like natural killer (NK) cells, NKT cells, or dendritic cells as has previously been published [15, 16].

A recent study involved the role of lower respiratory tract infections and an increased risk of recurrent wheezing and subsequent asthma in preschool children [17]. There is increasing evidence of asthma pathogenesis and events occurring during early childhood, especially viral respiratory tract infections and their interactions with this microbiome. PID patients present immune alterations associated with a significant number of infections, especially in the lower respiratory tract. Therefore, an-

other possibility for this minor allergen sensitization could be the development of respiratory symptoms similar to asthma and rhinitis, that may be related to inflammatory activation due to infectious processes but not to the IgE-mediated mechanism that is present in the majority of children diagnosed with asthma.

Our report has limitations, including the different diagnoses of PID patients in our cohort and the total number of patients. However, we do not consider these limitations to have influenced the final results and discussion.

In conclusion, we observed the frequency of allergenic sensitization in the group of patients with PID and symptoms suggestive of asthma, rhinitis, or atopic dermatitis to be lower than that found in the general population.

This is probably due the impairment of IgE formation secondary to the immunologic alteration.

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Disclosure Statement

The authors declare that there are no conflicts of interest to disclose.

References

- 1 Picard C, Al-Herz W, Bousfiha A, et al: Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency, 2015. *J Clin Immunol* 2015;35:696–726.
- 2 Rezaei N, Bonilla FA, Sullivan KE, de Vries E, Orange JS: An introduction to primary immunodeficiency diseases; in Rezaei N, Aghamohammadi A, and Notarangelo LD (eds): *Primary Immunodeficiency Diseases*, ed 5. Berlin, Springer, Germany 2008, pp 1–38.
- 3 Boyle JM, Buckley RH: Population prevalence of diagnosed primary immunodeficiency diseases in the United States. *J Clin Immunol* 2007;27:497–502.
- 4 Lourenço DB, Munhoz DC, Bariani DB, et al: Prevalence of allergic rhinitis in IgA deficiency. *Arq Med Hosp Fac Cienc Med Santa Casa São Paulo* 2012;57:63–66.
- 5 Azizi G, Ahmadi M, Abolhassani H, et al: Autoimmunity in primary antibody deficiencies. *Int Arch Allergy Immunol* 2016;171:180–193.
- 6 Soares FA, Segundo GR, Alves R, Ynoue LH: Indoor allergen sensitization profile in allergic patients of the allergy clinic in the University Hospital in Uberlândia, Brazil. *Rev Assoc Med Bras* 2007;53:25–28.
- 7 Motta AA, Kalil J, Barros MT: Cutaneous tests. *Rev Bras Alerg Immunopatol* 2005;28:73–83.
- 8 Asher MI, Keil U, Anderson HR, et al: International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;8:483–491.
- 9 Costa-Carvalho BT, Sano F, Rosario NA, Condino-Neto A, Solé R: Primary immunodeficiencies in the allergy practice in Brazil. *Rev Bras Alerg Immunopatol* 2011;34:241–250.
- 10 Ramírez-Vargas N, Arabin-Oropeza SE, Mojica-Martínez D et al: Clinical and immunological features of common variable immunodeficiency in Mexican patients. *Allergol Immunopathol (Madr)* 2014;42:235–240.
- 11 Leiva LE, Zelazco M, Oleastro M, et al: Primary immunodeficiency diseases in Latin America: the second report of the LAGID registry. *J Clin Immunol* 2007;27:101–108.
- 12 Edgar JD, Buckland M, Guzman D, et al: The United Kingdom Primary Immune Deficiency (UKPID) Registry: report of the first 4 years' activity 2008–2012. *Clin Exp Immunol* 2014;175:68–78.
- 13 Özcan C, Metin A, Erkoçoğlu M, Kocabaş CN: Allergic diseases in children with primary immunodeficiencies. *Turk J Pediatr* 2014; 56:41–47.
- 14 Agondi RC, Barros MT, Kokron CM et al: Can patients with common variable immunodeficiency have allergic rhinitis? *Am J Rhinol Allergy* 2013;27:79–83.
- 15 Kaneko K, Wang Z, Kim SH, Morelli AE, et al: Dendritic cells genetically engineered to express IL-4 exhibit enhanced IL-12p70 production in response to CD40 ligation and accelerate organ allograft rejection. *Gene Ther* 2003;10:143–512.
- 16 Leite-de-Moraes MC, Dy M: Natural killer T cells: a potent cytokine-producing cell population. *Eur Cytokine Netw* 1997;8:229–237.
- 17 Kwong CG, Bacharier LB: Microbes and the role of antibiotic treatment for wheezy lower respiratory tract illnesses in preschool children. *Curr Allergy Asthma Rep* 2017;17:34.