ORIGINAL ARTICLE

Atopic Manifestations Are Underestimated Clinical Features in Various Primary Immunodeficiency Disease Phenotypes

de Wit J[1], Dalm VASH[2,3]*, Totté JEE[1]*, Kamphuis LSJ[4], Vermont CL[5], van Osnabrugge FY[1], van Hagen PM[2,3], Pasmans SGMA[1,6] on behalf of the Academic Centers for Allergic Diseases and the Rare Immunological Disease Centre

[1]Department of Dermatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[2]Department of Internal Medicine, Division of Clinical Immunology, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[3]Department of Immunology, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[4]Department of Pulmonary Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[5]Department of Pediatrics, Division of Infectious Diseases and Immunology, Erasmus MC University Medical Center-Sophia Children's Hospital, Rotterdam, The Netherlands
[6]Department of Dermatology, Erasmus MC University Medical Center-Sophia Children's Hospital-Center of Pediatric Dermatology, Rotterdam, The Netherlands
*These authors contributed equally to this work.

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Abstract

Background: Atopic manifestations are described as a clinical feature of various primary immunodeficiency disease (PID) phenotypes and are frequently reported in combined immunodeficiencies. The prevalence of atopic manifestations in other PIDs remains largely unknown.
Objective: To evaluate the prevalence of atopic manifestations in PIDs other than combined immunodeficiencies and to identify in which PIDs atopic manifestations are most common with the aim of improving patient care.
Methods: A partner-controlled, questionnaire-based study was performed in pediatric and adult PID patients. Data from diagnostic tests to assess atopic manifestations (ie, diagnostic criteria for atopic dermatitis, spirometry, specific IgE against food and inhalant allergens) were collected from adult patients to confirm patient-reported atopic manifestations.
Results: Forty-seven children and 206 adults with PIDs and 56 partner-controls completed the questionnaire. Thirty-five pediatric patients (74.5%) and 164 adult patients (79.6%) reported having experienced 1 or more atopic manifestations compared with 28 partner-controls (50.0%). In the comparison of adult patients with partner-controls, prevalence values were as follows: atopic dermatitis, 49.5% vs 27.3% (P=.003); food allergy, 10.7% vs 1.9% (P=.031); asthma, 55.7% vs 14.8% (P<.001); and allergic rhinitis, 49.8% vs 21.8% (P<.001). The frequency of current atopic manifestations reported by patients was higher than the prevalence based on diagnostic tests (atopic dermatitis, 11.2%; food allergy, 1.9%; asthma 16.4%; and allergic rhinitis, 11.5%).
Conclusion: Atopic manifestations are prevalent clinical features across a broad spectrum of PIDs and, in our cohort, frequently present in patients with combined immunodeficiencies and predominant antibody deficiencies. Atopic manifestations should be evaluated in patients with PIDs.

Key words: Asthma. Atopic dermatitis. Food hypersensitivity. Immunologic deficiency syndromes. Seasonal allergic rhinitis.

Resumen

Antecedentes: En varios de los fenotipos asociados a las inmunodeficiencias primarias (PID), se describen, frecuentemente, diversas manifestaciones atópicas, en particular, en la inmunodeficiencia combinada. Sin embargo, la prevalencia de las manifestaciones atópicas en otras PID sigue siendo desconocida.
Objetivo: Calcular la prevalencia de las manifestaciones atópicas en otras PID e identificar en cuáles de éstas son las más frecuentes con el fin de mejorar la atención a los pacientes.
Métodos: Se realizó un estudio basado en un cuestionario validado, tanto en pacientes pediátricos como en adultos diagnosticados de PID. Posteriormente, se recopilaron los resultados de diferentes pruebas diagnósticas para enfermedades atópicas con el fin de corroborar los síntomas notificados por los pacientes adultos; es decir, criterios de diagnóstico para la dermatitis atópica, espirometría e IgE específica contra alérgenos alimentarios e inhalados.
Resultados: El cuestionario se completó por 47 niños y 206 adultos con PID, y por 56 controles. Treinta y cinco pacientes pediátricos (74,5%) y 164 adultos (79,6%) informaron haber experimentado alguna vez una o más manifestaciones atópicas en comparación con

28 controles (50,0%). En los pacientes adultos, al comparar la prevalencia con sus controles, se observaron los siguientes resultados, respectivamente: dermatitis atópica 49,5% *vs.* 27,3% (p = 0,003); alergia alimentaria 10,7% *vs.* 1,9% (p = 0,031); asma 55,7% *vs.* 14,8% (p <0,001); y rinitis alérgica 49,8% frente a 21,8% (p <0,001). La frecuencia de manifestaciones atópicas objetivadas en los pacientes fue superior a la prevalencia basada en las pruebas diagnósticas (dermatitis atópica 11,2%, alergia alimentaria 1,9%, asma 16,4% y rinitis alérgica 11,5%).
Conclusión: Las manifestaciones atópicas son frecuentes en un amplio espectro de PID. En nuestra cohorte se presentaron con mayor frecuencia en los pacientes con inmunodeficiencia combinada y deficiencias predominantes de anticuerpos. Por lo tanto, se debe realizar una evaluación de las manifestaciones atópicas en los pacientes con PID.

Palabras clave: Asma. Dermatitis atópica. Hipersensibilidad alimentaria. Inmunodeficiencias. Rinitis alérgica estacional.

Summary box

- **What do we know about this topic?**

  Atopic manifestations are described as a clinical feature of various primary immunodeficiency disease phenotypes and are frequently reported in combined immunodeficiencies. However, the prevalence of atopic manifestations in other primary immunodeficiency diseases is largely unknown.

- **How does this study impact our current understanding and/or clinical management of this topic?**

  The care of patients with a combined immunodeficiency or predominantly antibody deficiency could be improved by systematic evaluation of atopic manifestations. As atopic manifestations are common clinical features in primary immunodeficiency diseases, evaluation of these symptoms should be considered.

Introduction

Primary immunodeficiency diseases (PIDs) encompass a heterogeneous group of more than 300 inheritable defects of immunity caused by variants in genes encoding functional proteins of human immune cells [1,2]. The incidence of symptomatic PIDs is estimated at 1 in 2000 live births, with a prevalence of 1 in 10 000-12 000 in the general population [2-4]. PIDs are typically characterized by recurrent and/or severe infections. Additionally, patients may have autoimmunity, autoinflammation, malignancy, and allergic disorders [5-7]. Allergic manifestations may be part of the so-called atopic syndrome, which is characterized by atopic dermatitis (AD), food allergy (FA), asthma, and allergic rhinitis (AR).

Atopic manifestations are a clinical feature of various PID phenotypes [2,8,9]. Nonetheless, one narrative review reported the presence of these manifestations mainly in deficiencies affecting both cellular and humoral immunity (combined immunodeficiencies [CIDs]), such as DOCK8 deficiency, and CIDs with associated or syndromic features, such as Comèl Netherton syndrome [8]. Other original studies also reported atopic manifestations, mainly in patients with CIDs and at lower frequencies, comparable to the prevalence reported for the general population, in predominant antibody deficiencies (PADs), such as selective immunoglobulin (Ig) A deficiency [9]. However, original data on atopic manifestations in PIDs are limited, as patient samples are small, and the diagnosis of atopic manifestations is generally based on medical records rather than diagnostic tests or the data source was not described.

The development of atopic manifestations within atopic syndrome is the result of a genetic predilection toward producing specific IgE (sIgE) following exposure to allergens [10]. In this process, presentation of processed allergen to T lymphocytes by antigen-presenting cells leads to activation of B lymphocytes and subsequent production of sIgE [11]. Although the pathogenesis of atopic manifestations is complex and multifactorial, the pathogenic pathway could overlap with the pathways involved in some PIDs [12]. For example, mutations in the *SPINK5* gene can cause both Comèl Netherton syndrome and atopy. This genetic overlap might, therefore, explain the presence of atopic manifestations in patients with specific PIDs.

Early recognition and treatment of atopic manifestations in patients with PIDs could prevent clinical deterioration. The diagnostic delay for asthma is still 3.3 years [13]. The airways of untreated asthma patients become chronically swollen, and persistence of AR can lead to sleep loss and secondary impaired cognitive functioning [14,15]. Furthermore, the long-term presence of untreated atopic manifestations may contribute to the development of other, related disease processes, including sinusitis, and a lower quality of life [15].

The aim of this study was to compare the prevalence of atopic manifestations in children and adults affected by a PID with findings for partner-controls by using a questionnaire and diagnostic tests in order to identify patients with specific PIDs who are more likely to develop atopic syndrome.

Methods

Study Design

We performed a cross-sectional partner-controlled questionnaire-based study to determine the prevalence of atopic manifestations in patients with PIDs. In addition, standard care data on diagnostic tests for AD, FA, asthma and AR were retrospectively and prospectively collected for adult patients to confirm the patient-reported atopic manifestations. The study was designed and conducted by the Department of Dermatology, Department of Internal Medicine, Division of Clinical Immunology, and Department of Pediatrics, Division of Infectious Diseases of the Erasmus MC University Medical Center, Rotterdam, The Netherlands. The study procedures were approved by the institutional review board of the Erasmus MC University Medical Center (MEC-2018-1260). All patients aged 16 years or older provided written informed consent themselves. For children below 12 years, either the parents or guardians signed, and for children aged 12-16 years both the adolescent and parents/caregivers signed, in accordance with Dutch law.

Study Population

Patients of all ages diagnosed with a PID according to Picard et al [1] were included. We selected patients from an ongoing database of the Department of Internal Medicine, Division of Clinical Immunology, and Department of Pediatrics, Division of Infectious Diseases, Erasmus MC University Medical Center, which prospectively registers all patients diagnosed with a PID (MEC-2013-026). We included patients enrolled in this database between 2013 and September 2018. Patients who underwent curative hematopoietic stem cell transplantation and patients (or their parent[s]/caregiver[s]) who were not able to read or understand the Dutch language were excluded from this study. The control group consisted of partners of adult patients who completed the questionnaire and were not deceased in order to correct for environmental factors regardless of genetic influences, which might be involved in the atopic manifestations of PIDs.

Outcome Measures

The primary outcome measure was the self-reported prevalence of current and previous atopic manifestations in children (by parent/caregiver) and adults (≥18 years) with a PID. The findings were compared with those of adult partner-controls. Secondary outcomes were age at onset of the first atopy-associated symptoms and verification of atopic manifestation using diagnostic criteria or tests. To assess the self-reported or parent-reported (patients <12 years) prevalence of AD, asthma, and AR, we used the Phase Three Core Questionnaire of the International Study of Asthma and Allergies in Childhood (ISAAC) (Appendix 1) [16]. Asthma data from patients <5 years were not taken into account for further analysis. The prevalence of FA was estimated based on a doctor's diagnosis or double-blind, placebo-controlled food challenge (both reported by the patient).

Data from the questionnaires of adult patients were verified against retrospectively and prospectively collected standard care data. The diagnosis of AD was confirmed based on the United Kingdom Working Party Diagnostic Criteria for Atopic Dermatitis by a dermatologist or immunologist at the outpatient clinic [17-19]. The diagnosis of asthma was confirmed based on spirometry with either a bronchodilator reversibility test or a bronchial challenge test with histamine. Asthma was defined according to the Global Initiative for Asthma (GINA) guidelines as an FEV_1/FVC ratio below the lower limit of normal at least once during the diagnostic process, the presence of symptoms, and an increase of ≥12% and ≥200 mL from baseline in FEV_1 after inhaling a bronchodilator, or a positive provocation test result [20]. Additionally, asthma was classified as allergic when sIgE against a panel of inhalant allergens was ≥0.35 kU/L and sIgE against at least 1 specific inhalant allergen was ≥0.35 kU/L. The diagnoses of FA and AR were verified using sIgE against a panel of food allergens and a panel of inhalant allergens, respectively. As the presence of sIgE to a specific allergen does not necessarily equate to a clinically relevant allergic response to that substance, FA was confirmed if a patient reported an FA that was diagnosed by a doctor or based on a double-blind, placebo-controlled food challenge combined with sensitization for food allergens, ie, sIgE against the allergen panel of ≥0.35 kU/L and sIgE against at least 1 specific allergen of ≥0.35 kU/L. Additionally, AR was confirmed if a patient reported previous hay fever combined with sensitization to inhalant allergens, ie, sIgE of ≥0.35 kU/L against the panel of allergens and sIgE of ≥0.35 kU/L against at least 1 specific allergen.

Study Procedures

A questionnaire was sent by mail to 80 pediatric and 359 adult patients with PIDs between October 2017 and September 2018 (Appendix 2-5). Standard care data on the diagnosis of atopic manifestations were collected from the electronic patient record until August 2019. Biochemical data, ie, sIgE against inhalant allergens and food allergens, collected before August 2009, were not used.

Statistical Analysis

The prevalence of atopic manifestations is presented as mean (SD) for normally distributed continuous data or, otherwise, as median (IQR). The difference in the prevalence of previous atopic manifestations between adult patients and partner-controls was analyzed using the χ^2 test. Basic descriptive statistics and tests were performed using IBM SPSS for Windows, Version 25.0 (IBM Corp).

Results

Study Population Characteristics

The questionnaire was completed and returned by 253 patients (57.6%; 47 children and 206 adults). Responders and nonresponders had comparable demographic and disease characteristics, although adult responders were older than adult nonresponders (data not shown). Most

Table 1. General Patient Demographics.

	Pediatric patients (n=47)	Adult patients (n=206)	Adult partner-controls (n=56)
Median (IQR) age, y	11.9 (7.3-15.7)	53.6 (37.5-64.6)	59.3 (46.2-69.8)[a]
Male sex, No (%)	33 (70.2)	83 (40.3)	34 (60.7)
Age PID diagnosis, y mean (SD)	4.6 (4.1)	41.9 (19.9)	Not applicable
IUIS phenotypic classification of PID, No. (%)			
Immunodeficiencies affecting cellular and humoral immunity	0 (0.0)	1 (0.5)	Not applicable
Combined immunodeficiencies with associated or syndromic features	1 (2.1)	7 (3.4)	
Predominantly antibody deficiencies	37 (78.7)	181 (87.9)	
- Common variable immunodeficiency	10 (21.3)	74 (35.7)	
- IgG subclass deficiency	2 (4.3)	34 (16.5)	
- Selective IgA deficiency	1 (2.1)	5 (2.4)	
- Selective antibody deficiency with normal immunoglobulins	0 (0.0)	26 (12.6)	
- X-linked agammaglobulinemia	4 (8.5)	7 (3.4)	
- Hypogammaglobulinemia	12 (25.5)	23 (11.2)	
- Hyper IgM syndrome	3 (6.4)	3 (1.5)	
- Combined antibody deficiency	0 (0.0)	7 (3.4)	
- Other	5 (10.6)	2 (1.0)	
Diseases of immune dysregulation	0 (0)	1 (0.5)	
Congenital defects of phagocyte number or function	3 (6.4)	2 (1.0)	
Defects in intrinsic and innate immunity	2 (4.3)	5 (2.4)	
Autoinflammatory disorders	2 (4.3)	4 (1.9)	
Complement deficiencies	0 (0)	1 (0.5)	
Phenocopies of inborn errors of immunity	0 (0)	1 (0.5)	
Unknown	2 (4.3)	3 (1.5)	

Abbreviations: IUIS, International Union of Immunological Societies; PID, primary immunodeficiency disease.
[a]Missing, n=3 (5.4%).

responders (n=218, 86.2%) had a PAD according to the 2017 International Union of Immunological Societies (IUIS) Phenotypic Classification for Primary Immunodeficiencies, including 37 children (78.7%) and 181 adults (87.9%) (Table 1) [21]. The median age of the patients included was 47.9 (24.1-61.1) years; children had a median age of 11.9 (7.3-15.7) years and adults of 53.6 (37.5-64.6) years. Males accounted for 116 patients (45.8%). Mean age at the time of diagnosis of the PID was 4.6 (4.1) years in pediatric patients and 41.9 (19.9) years in adult patients.

Control Group Characteristics

A questionnaire was sent to the partners of 201 adult patients, as 5 patients with a PID died after completing the questionnaire. Fifty-six (27.7%) questionnaires were completed by partner-controls, returned, and included for further analysis. Partner-controls had a median age of 59.3 (46.2-69.8) years, and 34 (60.7%) were male.

Atopic Manifestations in Children With a Primary Immunodeficiency Disease

Current atopic manifestations

At the moment of completing the questionnaire, 29 pediatric patients (61.7%) reported having had ≥1 atopic manifestation. The prevalence values were 19.1% for AD, 25.0% for FA, 30.4% for asthma, and 34.8% for AR.

Previous atopic manifestations

At least 1 previous atopic manifestation was reported by 35 (74.5%) pediatric patients, with the highest prevalence reported for AD (60.0%). Previous FA, asthma, and AR were reported by 25.0%, 34.8%, and 30.4% of the children, respectively (Table 2 and S1). Atopic manifestations were reported across the various phenotypes of PIDs. However, the most important conclusion on the prevalence of atopic manifestations could be drawn within the group of PADs owing to the large number of

Table 2. Atopic Manifestations in Primary Immunodeficiency Diseases.

	Pediatric patients (n=47)	Adult patients (n=206)	Adult partner-controls (n=56)	*P* Value[a]
Atopic dermatitis				
Current, No. (%)	9 (19.1)	22 (10.8)[4]	3 (5.5)[14]	.003
Previous, No. (%)	27 (60.0)[1]	100 (49.5)[5]	15 (27.3)[14]	
Diagnostic criteria[b], No. (%)		11 (11.2)[6]		
Food allergy				
Previously diagnosed, No. (%)	9 (25.0)[2]	18 (10.7)[7]	1 (1.9)[15]	.031
sIgE against food allergens ≥0.35 kU/L, No. (%)		5 (4.8)[8]		
Asthma				
Current, No. (%)	14 (30.4)[3]	93 (45.1)[4]	7 (13.0)[16]	<.001
Previous, No. (%)	16 (34.8)[3]	113 (55.7)[9]	8 (14.8)[16]	
Positive spirometry with bronchodilator reversibility test[c], No. (%)		10 (16.4)[12]		
Positive bronchial challenge test with histamine, No. (%)		6 (24.0)[13]		
Allergic rhinitis				
Current, No. (%)	16 (34.8)[3]	91 (45.1)[4]	9 (16.4)[14]	<.001
Previous, No. (%)	14 (30.4)[3]	102 (49.8)[12]	12 (21.8)[14]	
sIgE against inhalant allergens ≥0.35 kU/L, No. (%)		25 (19.2)[13]		

Missing: [1]n=2 (4.3%), [2]n=11 (23.4%), [3]n=1 (2.1%), [4]n=2 (1.0%), [5]n=4 (1.9%), [6]n=108 (52.4%), [7]n=37 (18.0%), [8]n=101 (49.0%), [9]n=3 (1.5%), [10]n=145 (70.4%), [11]n=181 (87.9%), [12]n=1 (0.5%), [13]n=76 (36.9%), [14]n=1 (1.8%), [15]n=3 (5.4%), [16]n=2 (3.6%).
[a]Difference in prevalence of previous atopic manifestations between adult patients and partner-controls.
[b]United Kingdom Working Party's Diagnostic Criteria for Atopic Dermatitis applied by a dermatologist or immunologist at the outpatient clinic [17-19].
[c]Positive was defined according to Global Initiative for Asthma (GINA) guidelines as an FEV_1/FVC ratio below the lower limit of normal and an increase of ≥12% and ≥200 mL from baseline in FEV_1 after inhaling a bronchodilator [20].

patients with this phenotype (Table 3). The complete spectrum of atopic manifestations was present in 6.4% of patients. The number of manifestations reported by the patients was 3, 2, and 1 in 12.8%, 21.3%, and 34.0%, respectively. Mean age at onset of the first atopy-associated symptom was 2.0 (3.1) years for AD, 2.6 (3.5) years for asthma, and 5.1 (4.1) years for AR. FA was diagnosed at a mean age of 1.8 (2.3) years.

Atopic Manifestations in Adults With a Primary Immunodeficiency Disease and Partner-Controls

Current atopic manifestations

At least 1 atopic manifestation was reported by 134 adult patients (65.0%) and 17 adult partner-controls (30.4%). The prevalence values were 10.8% for AD, 10.7% for FA, 45.1% for asthma, and 45.1% for AR (Table 2 and S2). The prevalence of current atopic manifestations in partner-controls was 5.5% for AD, 1.9% for FA, 13.0% for asthma, and 16.4% for AR (Table 2 and S3).

Previous atopic manifestations

A total of 164 patients (79.6%) reported having experienced ≥1 atopic manifestations. The prevalence was 49.5% for AD, 10.7% for FA, 55.7% for asthma, and 49.8% for AR (Table 2 and S2). Fifty percent (n=28) of partner-controls reported having experienced ≥1 atopic manifestation. Adult patients generally had a significantly higher prevalence of atopic manifestations than partner-controls. Partner-controls had AD in 27.3% of cases (*P*=.003), FA in 1.9% (*P*=.031), asthma in 14.8% (*P*<.001), and AR in 21.8% (*P*<.001) (Table 2 and S3). Atopic manifestations were reported across the various PID phenotypes. However, the most important conclusions on the prevalence of atopic manifestations could be drawn in CIDs with associated or syndromic features and PADs because of the large number of patients (Table 3). The complete spectrum of atopic manifestations was present in 4.4% of patients. Three, 2, or 1 manifestation was reported by 23.3%, 23.8%, and 28.3% of patients, respectively. None of the partner-controls reported the complete spectrum of atopic manifestations. Three, 2, or 1 atopic manifestations were reported by 5.4%, 5.4%, and 39.3% of the partner-controls, respectively. The first atopy-related symptom in patients was observed at a mean age of 23.4 (23.7) years in AD, 24.1 (20.9) years in FA, 20.2 (18.9) years in asthma, and 19.2 (11.7) years in AR. In controls, the corresponding ages were 28.9 (27.5), 24, 16.0 (15.8), and 23.0 (13.1) years, respectively.

Diagnostic Criteria and Tests for Atopic Manifestations

Skin inspection data were available from 98 patients, of whom 11 (11.2%) had been diagnosed with AD. Data

Table 3. Previous Atopic Manifestations According to IUIS Phenotypic Classification for Primary Immunodeficiency Diseases.

	Pediatric patients (n=47)	Adult patients (n=206)
Immunodeficiencies affecting cellular and humoral immunity, No. (%)	n=0	n=1
- Atopic dermatitis	-	0 (0.0)
- Food allergy	-	0 (0.0)
- Asthma	-	1 (100)
- Hay fever	-	0 (0.0)
Combined immunodeficiencies with associated or syndromic features, No. (%)	n=1	n=7
- Atopic dermatitis	0 (0.0)	4 (57.1)
- Food allergy	0 (0.0)1	2 (33.3)[5]
- Asthma	0 (0.0)	5 (71.4)
- Hay fever	0 (0.0)	5 (71.4)
Predominantly antibody deficiencies, No. (%)	n=37	n=181
- Atopic dermatitis	21 (60.0)[2]	91 (51.4)[6]
- Food allergy	7 (25.9)[3]	17 (11.6)[7]
- Asthma	15 (41.7)[4]	104 (58.1)[8]
- Hay fever	11 (29.7)[4]	95 (52.8)[9]
Diseases of immune dysregulation, No. (%)	n=0	n=1
- Atopic dermatitis	-	0 (0.0)
- Food allergy	-	0 (0.0)
- Asthma	-	0 (0.0)
- Hay fever	-	0 (0.0)
Congenital defects of phagocyte number or function, No. (%)	n=3	n=2
- Atopic dermatitis	2 (66.7)	1 (50.0)
- Food allergy	1 (33.3)	1 (50.0)
- Asthma	1 (33.3)	1 (50.0)
- Hay fever	3 (100.0)	0 (0.0)
Defects in intrinsic and innate immunity, No. (%)	n=2	n=5
- Atopic dermatitis	2 (100)	2 (40.0)
- Food allergy	0 (0.0)	0 (0.0)[10]
- Asthma	0 (0.0)	1 (20.0)
- Hay fever	0 (0.0)	1 (20.0)
Autoinflammatory disorders, No. (%)	n=2	n=4
- Atopic dermatitis	2 (100)	0 (0.0)
- Food allergy	1 (50.0)	0 (0.0)
- Asthma	0 (0.0)	0 (0.0)
- Hay fever	0 (0.0)	1 (25.0)
Complement deficiencies, No. (%)	n=0	n=1
- Atopic dermatitis	-	0 (0.0)
- Food allergy	-	0 (0.0)
- Asthma	-	0 (0.0)
- Hay fever	-	0 (0.0)

(continued)

Table 3. Previous Atopic Manifestations According to IUIS Phenotypic Classification for Primary Immunodeficiency Diseases *(continuation).*

	Pediatric patients (n=47)	Adult patients (n=206)
Phenocopies of inborn errors of immunity, No. (%)	n=0	n=1
- Atopic dermatitis	-	0 (0.0)
- Food allergy	-	0 (0.0)
- Asthma	-	0 (0.0)
- Hay fever	-	0 (0.0)
Unknown, No. (%)	n=2	n=3
- Atopic dermatitis	2 (100)	2 (66.7)
- Food allergy	0 (0.0)	0 (0.0)
- Asthma	0 (0.0)	1 (50.0)[11]
- Hay fever	0 (0.0)	0 (0.0)

Abbreviations: IUIS, International Union of Immunological Societies.
Missing: [1]n=1 (100%), [2]n=2 (5.4%), [3]n=10 (27.0%), [4]n=1 (2.7%), [5]n=1 (14.3%), [6]n=4 (2.2%), [7]n=34 (18.8%), [8]n=2 (1.1%), [9]n=1 (0.6%), [10]n=2 (20.0%), [11]n=1 (33.3%).

on sIgE against a panel of food allergens were available for 105 patients. Five patients (4.8%) had elevated sIgE levels (≥0.35 kU/L) against the panel. Within these patients, sIgE levels for 17 specific allergens were ≥0.35 kU/L, suggesting sensitization. Six food allergens in 2 patients (1.9%) were also reported by patients with FA based on a doctor's diagnosis or double-blind, placebo-controlled food challenge (both patient-reported), thus indicating true food allergy. Bronchodilator reversibility tests were performed in 61 patients and bronchial challenge tests with histamine in 25 patients. Based on the diagnostic tests, 11 patients (16.4%) had confirmed asthma, and almost half of these patients also reported previous asthma. Data on sIgE against a panel of inhalant allergens were available for 130 patients, of whom 25 (19.2%) had elevated sIgE levels (≥0.35 kU/L). The most prevalent specific inhalant allergens were house dust mite (*Dermatophagoides pteronyssinus*) (n=14), followed by grass pollen (n=12), birch tree pollen (n=9), cat dander (n=8), dog dander (n=7), mugwort pollen (n=5), and rabbit dander and horse dander (both n=1) (Table 2 and S2). Fifteen of these patients (11.5%) also reported having experienced hay fever, indicating true AR.

Discussion

This study demonstrates that atopic manifestations, including AD, FA, asthma, and AR, are prevalent in children and adults with PIDs. In adults, patient-reported previous atopic manifestations were significantly more common than in adult partner-controls. The atopic manifestations were reported across the various PID phenotypes. The most important conclusions can be drawn for CIDs and PADs (prevalence ranging from 11.6% for FA to 71.4% for asthma and AR) because of the high number of patients.

Ours is the first study to evaluate the prevalence of atopic manifestations in a cohort of children and adults with PID using both questionnaire data and diagnostic criteria or tests. Compared to previous reports, in which diagnosis of atopic manifestations was generally based on patient records or the data source was not described, we found a significantly higher prevalence of atopic manifestations in patients with PAD and comparable numbers of patients with atopic manifestations in CID [9].

The pathogenic pathway involved in development of atopic syndrome is characterized by autoallergy, in which atopy seems to stand at the boundary between allergy and autoimmunity, given the presence of IgE antibodies against self-proteins [22-24]. Based on this pathway, in which T lymphocytes play a central role, patients with a PID affecting cellular immunity, such as CID, might be more predisposed to develop atopic manifestations [12]. PADs, on the other hand, are generally characterized by failure of primary antibody production. A significant number of patients with common variable immunodeficiency disorder, the most prevalent PAD (38.5% of all PADs in our cohort), show disturbed T-lymphocyte function in addition to their primary humoral immunodeficiency, which could contribute to development of atopic syndrome [25]. Moreover, approximately one-third of patients with common variable immunodeficiency disorder have a clinical phenotype with autoimmunity, which is inversely correlated with CD8 cell proportions, again indicating a T-cell dysfunction [26]. However, the exact mechanism underlying the development of atopic manifestations in PIDs remains to be elucidated.

De Wit et al [12] previously identified 22 genes that are related to development of atopy but are also involved in PIDs. These genes included mainly disease-causing genes resulting in CIDs (n=10), defects in intrinsic and innate immunity (n=5), and diseases of immune dysregulation (n=5). Only 2 atopy-related genes were also associated with PADs. Furthermore, the T_H lymphocyte–mediated genetic pathway was shown to be involved in atopy, thus explaining the predominance of atopic manifestations in cellular immunodeficiencies.

Several aspects should be taken into account when interpreting the results of this study. Firstly, according to the atopic march, in which the course of atopic manifestations over time is characterized (generally starting with AD in infancy and followed by FA, asthma, and AR later in childhood), the prevalence of asthma and AR in pediatric patients with a PID might be underestimated due to the patients' age group [27]. Secondly, the prevalence of current FA, asthma, and AR reported by adult patients was significantly higher than the prevalence based on diagnostic test results. This discrepancy could be due to overreporting of clinical symptoms related to atopy, as in FA, in which only half of the patients who believe they are allergic to food actually have proven intolerance, or because PID patients commonly have asthma-like airway complaints regardless of a positive diagnostic test [28]. Furthermore, atopic manifestations have a relapsing-remitting course and specific progression over time; this is characterized by the atopic march, in which prevalence varies over time. Moreover, several patients with chronic obstructive pulmonary disease could have incorrectly reported the presence of current asthma as a result of comparable symptoms between both pulmonary conditions. This could also be the case in the discrepancy between current and previous AR in children, as current atopic manifestations were based on atopy-associated symptoms and previous manifestations were based on the diagnosis of atopy. Lastly, data from this study might not be applicable to all PID phenotypes because mainly patients with PADs were included in our cohort. However, since PADs represent the largest group of PIDs worldwide, our results are relevant to many patients with PIDs. Moreover, consistent with the literature, symptoms of the atopic syndrome were frequent in patients with CIDs, despite the low number of patients in this PID group. Additionally, as only patients in a tertiary referral center were included in this study, data might not be applicable for all patients with atopic manifestations.

We found that atopic manifestations seem to develop before diagnosis of PID (4.6 years earlier in pediatric patients and 41.9 years in adult patients). As atopic manifestations generally start in childhood, the older age at which the first atopy-associated symptoms were observed in this study (in both adult patients and partner-controls) could be considered an overestimation resulting from recall bias or because data were based on patient-reported outcomes.

In conclusion, this questionnaire-based study shows that patient-reported previous atopic manifestations are more prevalent in adult patients with PIDs than in partner-controls. In particular, patients with CIDs and PADs were shown to have a higher chance of developing atopic manifestations. We propose evaluation of patients with CIDs and PADs for atopic manifestations, including asthma, to prevent clinical deterioration. Future studies should attempt to identify specific characteristics of atopic manifestations in PIDs that may increase awareness of an underlying PID.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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SGMA Pasmans

Department of Dermatology
Erasmus MC University Medical Center-Sophia Children's Hospital-Center of Pediatric Dermatology Rotterdam, The Netherlands
Wytemaweg 80
3015 CN, Rotterdam, The Netherlands
E-mail: s.pasmans@erasmusmc.nl