

Atopic manifestations are underestimated clinical features in various primary immunodeficiency disease phenotypes

Short title: Atopic manifestations in primary immunodeficiency disease phenotypes

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Abstract

Background: Atopic manifestations are described as clinical feature of various primary immunodeficiency disease (PID) phenotypes and in particular frequently reported in the combined immune deficiencies. The prevalence of atopic manifestations in other PIDs remains largely unknown.

Objective: To evaluate the prevalence of atopic manifestations in other PIDs and to identify in which PIDs atopic manifestations are most common in order to improve patient care.

Methods: A partner-controlled questionnaire-based study was performed in pediatric and adult PID patients. Subsequently, data of diagnostic tests for atopic manifestations (i.e. diagnostic criteria for AD, spirometry, specific IgE against food and inhalant allergens) were collected in 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 (74.5%) pediatric and 164 (79.6%) adult patients reported to have ever experienced one or more atopic manifestations compared with 28 (50.0%) partner-controls. In adult patients vs. partner-controls, prevalence of atopic dermatitis was 49.5% vs. 27.3% ($p=0.003$), food allergy 10.7% vs. 1.9% ($p=0.031$), asthma 55.7% vs. 14.8% ($p<0.001$) and allergic rhinitis 49.8% vs. 21.8% ($p<0.001$). 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 in a large spectrum of PIDs and in our cohort frequently present in patients with combined immune deficiencies and predominant antibody deficiencies. Evaluation of atopic manifestations should be considered 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%).

Conclusiones: 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

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 2,000 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 suffer from autoimmunity, auto inflammation, 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 described as clinical feature of various PID phenotypes [2, 8, 9]. Nonetheless, a narrative review reported presence of these manifestations mainly in immune deficiencies affecting both cellular and humoral immunity (combined immune deficiencies; CIDs), like DOCK8 deficiency, and CIDs with associated or syndromic features, such as Comèl Netherton syndrome [8]. Other original studies also reported atopic manifestations most commonly in patients with CIDs and in lower frequencies, comparable to prevalence in the general population, in predominant antibody deficiencies (PADs), like selective immunoglobulin (Ig) A deficiency [9]. However, original data on atopic manifestations in PIDs are limited, as studies comprise small patientsamples, and the diagnosis of atopic manifestations is generally not based on diagnostic tests, but on medical records or the data source was not described.

The development of atopic manifestations within the atopic syndrome is the result of a genetic predilection to produce specific IgE (sIgE) following exposure to allergens [10]. In this process, presentation of processed allergen by antigen-presenting cells to T lymphocytes leads to activation of B lymphocytes and subsequent production of sIgE [11]. Although the pathogenesis of atopic manifestations is complex and multifactorial, its pathogenic pathway could overlap with pathways involved in (certain) PIDs [12]. For example, mutations in the *SPINK5* gene can cause both the 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. Currently, diagnostic delay for asthma is still 3.3 years [13]. Airways of untreated asthma patients become chronically swollen and persistence of AR can lead to sleep loss and secondary decreased overall cognitive functioning [14, 15]. Furthermore, long-term existence of

untreated atopic manifestations may contribute to development of other related disease processes, including sinusitis, and a lower quality of life [15].

The aim of this study is to evaluate the prevalence of atopic manifestations in children and adults with a PID compared to partner-controls by using a questionnaire and diagnostic tests in order to identify specific PIDs with a higher chance of developing the atopic syndrome.

Material and Methods

Study design

We performed a cross-sectional partner-controlled questionnaire-based study on the prevalence of atopic manifestations in patients with PIDs. Furthermore, standard care data on diagnostic tests for AD, FA, asthma and AR were retrospectively and prospectively collected in 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, both parents or guardians signed, and for children aged 12-16 years both the adolescent and both parents or caregivers signed, in accordance with the Dutch law.

Study population

Patients of all ages with a PID diagnosis according to Picard *et al.* were included [1]. 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, that 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 a curative hematopoietic stem cell transplantation and patients (or their parent(s)/caregiver(s)) who were not able to read and 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 development of atopic manifestations in PIDs.

Outcome measurements

The primary outcome of the study was the self-reported prevalence of current and ever experienced atopic manifestations in children (by parent/caregiver) and adults (≥ 18 years) with a PID compared to adult partner-controls. Secondary outcomes were the age of 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, the Phase Three Core Questionnaire of the International Study of Asthma and Allergies in Childhood (ISAAC) was used (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 diagnosis or double-blind, placebo-controlled food challenge (both reported by the patient).

Data from the questionnaires of adult patients were verified using 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]. Spirometry with either a bronchodilator reversibility test or a bronchial challenge test with histamine was used to confirm the diagnosis of asthma. Asthma was defined according to Global Initiative for Asthma (GINA) guidelines as at least once during the diagnostic process the FEV1/FVC ratio was below the lower limit of normal, the presence of symptoms, and an increase of $\geq 12\%$ and ≥ 200 mL from baseline in FEV1 after inhaling a bronchodilator, or a positive provocation test [20]. Additionally, asthma was classified as allergic in case of both sIgE against a panel of inhalant allergens of ≥ 0.35 kU/L and sIgE against at least one specific inhalant allergen of ≥ 0.35 kU/L. For verification of the diagnoses FA and AR we used sIgE against a panel of food allergens and a panel of inhalant allergens, respectively. As 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 a FA that was diagnosed by a doctor or with a double-blind, placebo-controlled food challenge combined with sensitization for food allergens, i.e. sIgE against the panel of allergens of ≥ 0.35 kU/L and sIgE against at least one specific allergen of ≥ 0.35 kU/L. Additionally, AR was confirmed if a patient reported ever having hayfever combined with sensitization for inhalant allergens, i.e. sIgE against the panel of allergens of ≥ 0.35 kU/L and sIgE against at least one specific allergen of ≥ 0.35 kU/L.

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, i.e. sIgE against inhalant allergens and food allergens, collected before August 2009 were not used.

Statistical analysis

The prevalence of atopic manifestations were presented as mean and standard deviation (SD) for normally distributed continuous data or otherwise as median and interquartile range (IQR). The difference in the ever experienced prevalence of atopic manifestations between adult patients and partner-controls was analyzed using a Chi-Square test. Basic descriptive statistics and tests were performed using SPSS version 25.0 for Windows (IBM Corporation, Armonk, NY).

Results

Study population characteristics

Two hundred and fifty-three patients completed and returned the questionnaire (57.6%; 47 children and 206 adults). Responders and non-responders had comparable demographic and disease characteristics, but adult responders had a higher age compared with adult non-responders (data not shown). The majority of the responding patients (n=218, 86.2%) had a PAD according to the 2017 International Union of Immunological Societies (IUIS) Phenotypic Classification for Primary Immunodeficiencies, including 37 (78.7%) children and 181 (87.9%) adults (Table I)[21]. Median age of the included patients was 47.9 (IQR 24.1-61.1) years; children had a median age of 11.9 (IQR 7.3-15.7) years and adults of 53.6 (IQR 37.5-64.6) years. One hundred and sixteen (45.8%) patients were male. Mean age at time of diagnosis of the PID was 4.6 (SD 4.1) years in pediatric patients and 41.9 (SD 19.9) years in adult patients.

Control group characteristics

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

Atopic manifestations in children with a primary immunodeficiency disease

Current atopic manifestations

Twenty-nine (61.7%) pediatric patients reported to suffer from one or more atopic manifestations at the moment of completing the questionnaire. AD had a prevalence of 19.1%, FA of 25.0%, asthma of 30.4% and AR of 34.8%.

Ever experienced atopic manifestations

At least one ever experienced atopic manifestation was reported by 35 (74.5%) pediatric patients, of which AD (60.0%) had the highest prevalence. Ever experienced FA, asthma and AR were reported by 25.0%, 34.8% and 30.4% of the children, respectively (Table II and S1). Atopic manifestations were reported in a large spectrum of PIDs across the various phenotypes. However, the most important conclusion on the prevalence of atopic manifestations could be drawn within the group of PADs due to the large number of patients in this phenotype group (Table III). The complete spectrum of atopic manifestation was present in 6.4% of the patients. Three, two or one manifestation were reported by 12.8%, 21.3% and 34.0% of the patients, respectively. Mean age of onset of the first atopy-associated symptom was 2.0 (SD 3.1) years for AD, 2.6 (SD 3.5) years for asthma and 5.1 (SD 4.1) years for AR. FA was diagnosed at a mean age of 1.8 (SD 2.3) years.

Atopic manifestations in adults with a primary immunodeficiency disease and partner-controls

Current atopic manifestations

At least one atopic manifestation at the moment of completing the questionnaire was reported by 134 (65.0%) adult patients and 17 (30.4%) adult partner-controls. AD had a prevalence of 10.8%, FA of 10.7%, asthma of 45.1% and AR of 45.1% (Table II 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 II and S3).

Ever experienced atopic manifestations

A total of 164 (79.6%) patients reported to have ever experienced one or more atopic manifestations. AD showed a prevalence of 49.5%, FA of 10.7%, asthma of 55.7% and AR of 49.8% (Table II and S2). Fifty percent (n=28) of partner-controls reported to have ever experienced at least one atopic manifestation. Adult patients generally had a significantly higher prevalence of atopic manifestations as compared with partner-controls. Partner-controls showed AD in 27.3% ($p=0.003$), FA in 1.9% ($p=0.031$), asthma in 14.8% ($p<0.001$) and AR in 21.8% ($p<0.001$) (Table II 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 the CIDs with associated or syndromic features and PADs because of the large number of patients (Table III). The complete

spectrum of atopic manifestation was present in 4.4% of the patients. Three, two or one manifestation was reported by 23.3%, 23.8% and 28.3% of the patients, respectively. None of the partner-controls reported the complete spectrum of atopic manifestations. Three, two or one 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 (SD 23.7) years in AD, 24.1 (SD 20.9) years in FA, 20.2 (SD 18.9) years in asthma and 19.2 (SD 11.7) years in AR. In controls, corresponding ages were 28.9 (SD 27.5), 24, 16.0 (SD 15.8) and 23.0 (SD 13.1) years, respectively.

Diagnostic criteria and tests on atopic manifestations

Data on inspection of the skin was available from 98 patients, of which 11 (11.2%) patients were diagnosed with AD. Data on sIgE against a panel of food allergens was known for 105 patients. Five (4.8%) patients 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 within two (1.9%) patients were also reported by patients with a FA based on doctor diagnosis or double-blind, placebo-controlled food challenge (both patient-reported), which indicates a 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 (16.4%) patients had confirmed asthma, of which half of the patients reported to have ever experienced asthma as well. Data on sIgE against a panel of inhalant allergens was known for 130 patients, of which 25 (19.2%) patients had elevated sIgE levels (≥ 0.35 kU/L). 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), rabbit dander and horse dander (both n=1) (Table II and S2). Fifteen (11.5%) of these patients also reported ever experienced hayfever in the questionnaire, indicating true AR.

Discussion

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

This is the first study evaluating the prevalence of atopic manifestations in a cohort of children and adults with a 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 a PAD and comparable numbers of patients with atopic manifestations in CIDs [9].

The pathogenic pathway involved in development of the atopic syndrome could be characterized by autoallergy, in which atopy seems to stand at the boundary between allergy and auto-immunity, 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 CIDs, might be more predisposed to developing atopic manifestations [12]. PADs, on the other hand, are generally characterized by a primary antibody production failure. A significant number of patients with common variable immunodeficiency disorder (CVID), the most prevalent PAD (38.5% of all PADs in our cohort), shows also disturbed T lymphocyte function in addition to their primary humoral immunodeficiency, which could contribute to development of the atopic syndrome [25]. Moreover, approximately one third of the CVID patients have a clinical phenotype with autoimmunity, which is inverse correlated with CD8 cell proportions, indicating a T cell dysfunction as well [26]. However, the exact mechanism underlying the development of atopic manifestations in PIDs remains to be elucidated.

De Wit *et al.* previously identified 22 genes that are related to development of atopy, but are also involved in PIDs [12]. 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 two atopy-related genes were also associated with PADs. Furthermore, the Th lymphocyte-mediated genetic pathway was identified to be involved in atopy, which could explain 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 age of these patients [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 over reporting clinical symptoms related to atopy, as is known from FA,

in which only half of the patients that believe they are allergic to food actually have a 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 a specific progression over time, characterized by the atopic march, resulting in a time-varying prevalence. Moreover, a number of patients with chronic obstructive pulmonary disease could have incorrectly reported 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 ever experienced AR in children as current atopic manifestations were extracted based on atopy-associated symptoms and ever experienced manifestations based on the atopy diagnosis. Lastly, data from this study might not be applicable to all PID phenotypes because mainly patients with PADs were included in our cohort. However, PADs represent the largest group of PIDs worldwide and, therefore, our results are relevant to a large number of patients with PIDs. Moreover, symptoms of the atopic syndrome were frequently reported in patients with CIDs, which is in accordance with current literature, 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.

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

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

Conflict of interest disclosure

JdW, VD, JT, LK, CV, FvO, MvH and SP have no conflict of interest to declare.

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Tables

Table I. General patient demographics

	Pediatric patients (n=47)	Adult patients (n=206)	Adult partner-controls (n=56)
Age median (IQR)	11.9 (7.3-15.7)	53.6 (37.5-64.6)	59.3 (46.2-69.8) ¹
Sex, male n (%)	33 (70.2)	83 (40.3)	34 (60.7)
Age PID diagnosis, years mean (SD)	4.6 (4.1)	41.9 (19.9)	Not applicable
IUIS phenotypic classification of PID, n (%)			
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; IQR, interquartile range; n, number; PID, primary immunodeficiency disease. Missings: ¹ n=3 (5.4%).			

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Table II. Atopic manifestations in primary immunodeficiency diseases'

	Pediatric patients (n=47)	Adult patients (n=206)	Adult partner-controls (n=56)	p-value*
Atopic dermatitis				
Current, n (%)	9 (19.1)	22 (10.8) ⁵	3 (5.5) ¹⁵	0.003
Ever experienced, n (%)	27 (60.0) ¹	100 (49.5) ⁶	15 (27.3) ¹⁵	
Diagnostic criteria [†] , n (%)		11 (11.2) ⁷		
Food allergy				
Ever diagnosed, n (%)	9 (25.0) ²	18 (10.7) ⁸	1 (1.9) ¹⁶	0.031
sIgE against food allergens ≥ 0.35 kU/L, n (%)		5 (4.8) ⁹		
Asthma				
Current, n (%)	14 (30.4) ⁴	93 (45.1) ⁵	7 (13.0) ¹⁷	<0.001
Ever experienced, n (%)	16 (34.8) ⁴	113 (55.7) ¹⁰	8 (14.8) ¹⁷	
Positive spirometry with bronchodilator reversibility test [‡] , n (%)		10 (16.4) ¹¹		
Positive bronchial challenge test with histamine, n (%)		6 (24.0) ¹²		
Allergic rhinitis				
Current, n (%)	16 (34.8) ⁴	91 (45.1) ⁵	9 (16.4) ¹⁵	<0.001
Ever experienced, n (%)	14 (30.4) ⁴	102 (49.8) ¹³	12 (21.8) ¹⁵	
sIgE against inhalant allergens ≥ 0.35 kU/L, n (%)		25 (19.2) ¹⁴		
Missings: ¹ n=2 (4.3%), ² n=11 (23.4%), ³ n=6 (12.8%), ⁴ n=1 (2.1%), ⁵ n=2 (1.0%), ⁶ n=4 (1.9%), ⁷ n=108 (52.4%), ⁸ n=37 (18.0%), ⁹ n=101 (49.0%), ¹⁰ n=3 (1.5%), ¹¹ n=145 (70.4%), ¹² n=181 (87.9%), ¹³ n=1 (0.5%), ¹⁴ n=76 (36.9%), ¹⁵ n=1 (1.8%), ¹⁶ n=3 (5.4%), ¹⁷ n=2 (3.6%).				
[†] United Kingdom Working Party's Diagnostic Criteria for Atopic Dermatitis applied by a dermatologist or immunologist at the outpatient clinic.[17-19]				
[‡] Positive was defined according to Global Initiative for Asthma (GINA) guidelines as a FEV1/FVC ratio below the lower limit of normal and an increase of $\geq 12\%$ and ≥ 200 mL from baseline in FEV1 after inhaling a bronchodilator.[20]				
*Difference in prevalence of ever experienced atopic manifestations between adult patients and partner-controls.				

Table III. Ever experienced atopic manifestation according to IUIS phenotypic classification for primary immunodeficiency diseases

	Pediatric patients (n=47)	Adult patients (n=206)
Immunodeficiencies affecting cellular and humoral immunity, n (%)	n=0	n=1
- Atopic dermatitis	-	0 (0.0)
- Food allergy	-	0 (0.0)
- Asthma	-	1 (100)
- Hayfever	-	0 (0.0)
Combined immunodeficiencies with associated or syndromic features, n (%)	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)
- Hayfever	0 (0.0)	5 (71.4)
Predominantly antibody deficiencies, n (%)	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
- Hayfever	11 (29.7) ⁴	95 (52.8) ⁹
Diseases of immune dysregulation, n (%)	n=0	n=1
- Atopic dermatitis	-	0 (0.0)
- Food allergy	-	0 (0.0)
- Asthma	-	0 (0.0)
- Hayfever	-	0 (0.0)
Congenital defects of phagocyte number or function, n (%)	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)
- Hayfever	3 (100.0)	0 (0.0)
Defects in intrinsic and innate immunity, n (%)	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)
- Hayfever	0 (0.0)	1 (20.0)
Autoinflammatory disorders, n (%)	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)
- Hayfever	0 (0.0)	1 (25.0)

Complement deficiencies, n (%)	n=0	n=1
- Atopic dermatitis	-	0 (0.0)
- Food allergy	-	0 (0.0)
- Asthma	-	0 (0.0)
- Hayfever	-	0 (0.0)
Phenocopies of inborn errors of immunity, n (%)	n=0	n=1
- Atopic dermatitis	-	0 (0.0)
- Food allergy	-	0 (0.0)
- Asthma	-	0 (0.0)
- Hayfever	-	0 (0.0)
Unknown, n (%)	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
- Hayfever	0 (0.0)	0 (0.0)
Missings: 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%).		

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