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Molecular sensitisation patterns to aeroallergens in a Mediterranean paediatric population and their clinical implications

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Abstract
Background: Environmental exposures, climate change, and lifestyle factors are key contributors to respiratory allergies. Understanding the connection between allergen exposure and the development of allergic diseases in early life is essential for identifying sensitization patterns and optimizing diagnostic and therapeutic strategies.
Objective: This study aims to characterize the allergic sensitization profile in a Mediterranean paediatric population using a component-resolved diagnosis (CRD) approach. Specifically, we analyse the prevalence and serodominance of aeroallergens, examine age-related sensitization patterns, and assess their implications for personalized allergen immunotherapy. Additionally, we highlight the need to incorporate the identified molecular allergens into standardized allergenic extracts to improve diagnostic accuracy and immunotherapy efficacy.
Methods: We conducted an observational, cross-sectional study including paediatric patients (0–15 years) diagnosed with allergic rhinitis, with or without asthma. Patients were classified according to disease severity following international guidelines. Skin prick tests were performed using standardized extracts, and specific IgE levels were determined with the multiplex assay Allergy Explorer 2 (ALEX2-MADX).
Results: A total of 47 patients were included (mean age: 7.5 years). Sensitization to house dust mites (HDM) was the most prevalent (74.5%), followed by pollen (57.4%) and animal epithelia (44.6%). The most frequently recognized allergens were Der p 23 (59.57%) for HDM, Ole e 1 (36.17%) for olive pollen, and Fel d 1 (27.7%) for cat epithelium. The highest IgE levels were observed in children aged 6–10 years. Polysensitization was present in 66% of patients, with frequent co-recognition of allergens from different sources. The findings emphasize the need to ensure that allergenic extracts used in diagnosis and immunotherapy contain relevant molecular components to enhance treatment precision.

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Conclusion: A detailed molecular characterization of allergic sensitization in paediatric patients provides valuable insights into aeroallergen exposure and its clinical implications. Our findings reinforce the importance of incorporating relevant molecular allergens into standardized diagnostic and therapeutic extracts to optimize patient management and improve the efficacy of allergen-specific immunotherapy.

Introduction

It is important to understand how environmental exposure affects the development of disease from gestation to adulthood. It is widely accepted that exposure to different environmental allergens plays a significant role in the origin of allergic diseases. The prevalence of allergic diseases is on the rise worldwide, but the sensitisation profile varies considerably between populations due to the diverse exposure of environmental substances to the human immune system.[1] A review of studies carried out in different populations worldwide, where all the subjects were sensitised to *Dermatophagoides*, reveals that recognition patterns vary not only depending on the geographical areas under consideration but also on the age of the individuals tested.[2] A significant amount of research has been conducted on this topic, with population-based studies on many patients, indicating that sensitisation to dust mites of the genus *Dermatophagoides* occurs at an early age, typically within the first two years of life.[3]

The varying patterns of sensitisation and their evolution over time enable more precise diagnosis, identification of the onset of sensitisation to different allergens, and the development of safe treatment strategies, such as immunotherapy with precision allergens.[4] This diagnostic strategy has a direct impact on the decision to select a specific allergen for inclusion in the immunotherapy product. This finding has been corroborated by numerous previous studies in which this approach has been employed.[5,6] A recent systematic review indicates that the composition of the diagnosis is altered in over 50% of cases where the diagnosis is made based on the components.[7]

The objective of this study was to establish the allergic exposome, as well as the prevalence and serodominance of the aeroallergens to which paediatric patients in a Mediterranean area are most frequently allergic. This was achieved through component-based diagnosis with an MADX platform (ALEX2). The present study thus aims to evaluate the age of sensitisation to each allergen, the association with the different patterns of allergic disease, the prevalence of each of the allergenic molecules, and to infer the optimal composition of an immunotherapy product.

Material and Methods

Selected patients

An observational, cross-sectional, single-centre study was designed. The study population comprised paediatric patients diagnosed with allergic pathology (rhinitis/rhinoconjunctivitis and/or asthma). Prospective recruitment of patients was based on three cohorts, according to patient age: under 5 years (15 patients), 5–10 years (16 patients), and 11–15 years (16 patients). Subjects were consecutively enrolled in the study from July 2023 to September 2023 following the provision of informed consent by their legal guardians.

Inclusion criteria were as follows: patients under the age of 15 who were attending the Paediatric Allergy Outpatient Clinic of the Hospital de Sagunto (Valencia, Spain) for the first time and who had been diagnosed with respiratory allergic pathology (rhinitis/rhinoconjunctivitis and/or asthma). The hospital serves a population of 200,000 inhabitants, of whom approximately 22,000 are under the age of 15. Most of this younger demographic resides in a rural setting. Exclusion criteria were as follows: paediatric subjects in whom skin prick tests are contraindicated, those who are or have been under treatment with specific immunotherapy, lack of cooperation or compliance, residence in the geographical area of the Department of Health for less than three years, and those who have been under treatment with drugs that interfere with the immune system. The study was approved by the research ethics committee of the Hospital de Sagunto on 6 March 2023. Approval was granted following the Standards of Good Clinical Practice and the ethical principles set out in the latest revision of the Declaration of Helsinki adopted by the World Medical Association.

Diagnosis

The study consisted of a single visit, which included a complete allergological evaluation, a standardised medical history, a clinical examination, and Skin Prick Tests (SPT) with the aeroallergen extract battery of the area (Immunotek SL laboratory extracts): *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Tyrophagus putrescentiae*, *Lepidoglyphus destructor*, *Alternaria alternata*, cat epithelium, dog epithelium, horse epithelium, *Platanus hispanica*, *Olea europaea*, *Cupressus*, Grass pollen mix, *Betula*, *Parietaria judaica*, and *Blattella germanica*.

The diagnosis was reached based on a compatible clinical history and a positive SPT for at least one of the allergens under study (SPT was considered positive when a papule 3 mm larger in diameter than the negative control was produced). Asthma was diagnosed based on the Spanish asthma management guideline GEMA 5.0, and its severity was classified according to the same guideline.[8]

In all patients with asthma, spirometry was performed when patient cooperation was possible. For the diagnosis of allergic rhinitis, the recommendations of the ARIA guidelines were followed.[9]

IgE analysis

Subsequently, serum was extracted for molecular specific IgE analysis by ALEX2, MADX, Vienna, Austria. This is an in vitro, multiplex, ELISA-based allergy test including total IgE, 117 extracts, and 178 molecular allergens. Values > 0.35 kUA/L were considered positive. Non-specific IgE antibodies against carbohydrate cross-reactive determinants (CCD) were automatically blocked.

Statistical analysis

A general description will be made for the whole population of individuals studied, along with separate descriptions by pathology and age group. All data were analysed using GraphPad Prism 10 (version 10.3.1). Descriptive analyses (mean, standard deviation, range, median, and percentages) were performed.

Results

A total of 47 patients were included in the present study. The distribution of patients according to various demographic, clinical, and allergic sensitisation variables, expressed in terms of the number of patients and percentage frequencies, is shown in Table 1.

Most of the patients were male, representing 68.1% (32/47) of the study population, while females constituted 31.9% (15/47). All patients presented with allergic rhinitis, most with moderate severity (74.5%), followed by mild in 17.0% of cases and severe in 8.5%. In addition, 55.3% of patients also had asthma. For asthma, the predominant severity was mild in 36.2% of cases, while 14.9% had moderate asthma, and 4.3% of patients were classified as having severe asthma.

In relation to allergic sensitisation, most patients were found to be sensitised to mites (74.5%), followed by pollen (57.4%), epithelia (44.6%), and fungi (14.9%).

The Venn diagram (Figure 1) shows a varied distribution in terms of monosensitisation and polysensitisation. A total of 16 patients (34%) were sensitised exclusively to a single allergenic source. The highest proportion of these patients were sensitised to mites, with 10 patients (21.3%), followed by monosensitisation to pollen with four patients (8.5%).

Table 1 Baseline clinical features of the sample.

Variable	Frequencies (%)					
Sex	Males (68.1)			Females (31.9)		
Clinical	Rinithis (100.0)			Asthma (55.3)		
	Mild (17.0)	Moderate (74.5)		Mild (36.2)	Moderate (14.9)	
	Severe (8.5)			Severe (4.3)		
Allergen sensitisation	Mites (74.5)	Pollen (57.4)		Epithelia (44.6)		Fungi (14.9)

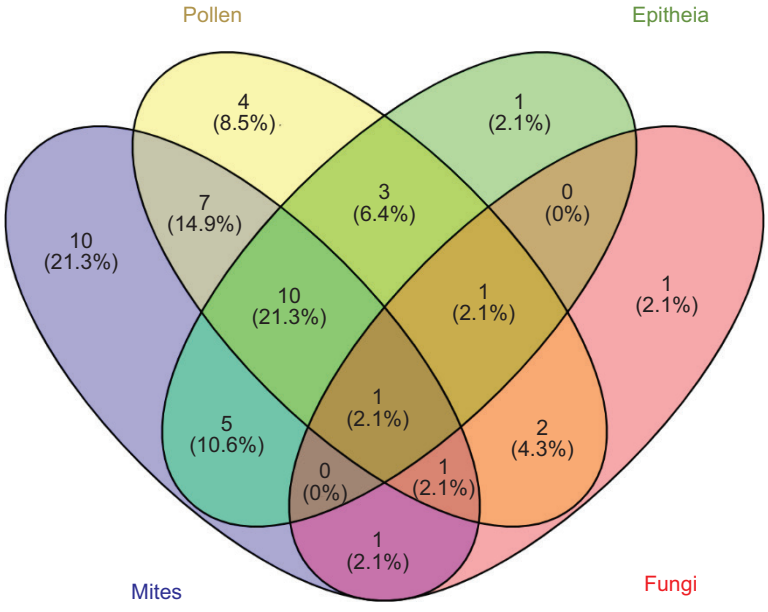

Figure 1 Venn diagram showing patterns of polysensitisation.

However, polysensitisation was predominant, affecting 66% of patients (31/47). The most frequent overlap was observed between mites, pollen, and epithelia, with 10 patients (21.3%) sensitised to these allergen sources. In addition, 7 patients (14.9%) were sensitised to both mites and pollen, followed by polysensitisation to mites and epithelia (10.6%) and pollen and epithelia (6.4%). Joint sensitisation to pollen and fungi was observed in only 2 patients (4.3%).

On the other hand, none of the patients were exclusively sensitised to the combination of epithelia and fungi. Finally, a single patient (2.1%) showed polysensitisation to all four allergenic sources, representing the most complex case of sensitisation.

IgE analysis

In the present study, allergic sensitisation was assessed by quantification of specific IgE in 47 patients divided into three age groups: 0–5 years, 6–10 years, and 11–15 years. IgE levels were measured for a wide variety of allergens, including mites, pollens, fungi, and animal epithelia. The results show a high prevalence of sensitisation to mite allergens, followed by pollens and epithelia, with a lower response to fungi. The distribution of specific IgE levels varies between age groups, although mite allergens stand out as the most common among the general population. IgE quantities are plotted on a heatmap (Figure 2A) detailing the individual patient's response to allergens, while Figure 2B summarises the mean IgE quantity for each allergen tested. Finally, Figure 2C presents the distribution of specific IgE levels according to age group, showing significant variations between the different age groups, with more pronounced responses in children older than 6 years.

Mites sensitisation

Sensitisation to mites was observed in most patients. IgE levels were determined against several mite allergen

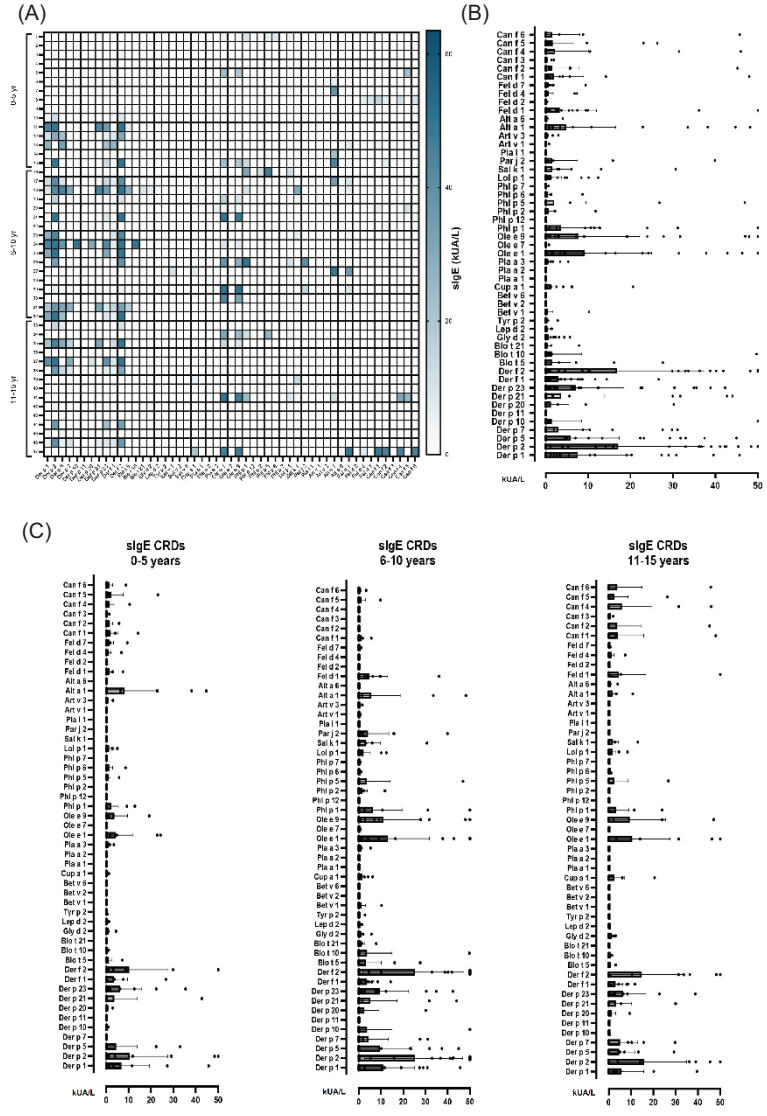

Figure 2 Analysis of specific IgE levels in 47 patients aged 0–15 years. (A) Heatmap of IgE levels to various allergens across three age groups: 0–5, 6–10 and 11–15 years. (B) Mean IgE levels (kUA/L) for each allergen in the total population. (C) IgE levels by age group for each allergen.

components, showing remarkable variability in recognition frequencies. *Der p 23* stood out with a frequency of 59.57%, being the mite allergen with the highest sensitisation rate in the study population. It was followed by *Der p 2* (51.06%), with an average sIgE of 17.10±20.72 kUA/L. *Der p 1* showed a mean sIgE level of 7.25±13.01 kUA/L, with a frequency of 42.6% of sensitised patients. Similarly, *Dermatophagoides farinae* allergens also showed high frequencies: *Der f 2* (51.06%) and *Der f 1* (38.30%). Notably, the group of children aged 6–10 years exhibited the highest levels of IgE to mites, reflecting a stronger sensitisation profile in this cohort.

Allergens with low recognition frequencies include *Der p 5* (25%), *Der p 7* (14.89%), *Der p 21* (12.28%), *Der p 20* (8.5%), *Der p 10* (8.51%), and *Blo t 5* (8.51%). The majority of patients who recognised these allergens exhibited clinical manifestations of rhinitis and asthma, suggesting a potential association between sensitisation to these components and allergic diseases. In addition, only three patients had IgE to *Lep d 2* and two patients had IgE to *Tyr p 2*, with a frequency of 6.4% and 4.3%, respectively, while *Der p 11* was not recognised by any of the patients.

Pollen sensitisation

The most frequently recognised pollen sources in this population belong to the families Oleaceae, Poaceae, Cupressaceae, and Platanaceae. However, sensitisation to the olive tree has the highest frequency (51.4%). Specifically, *Ole e 1* is one of the most prevalent allergens in all groups, with 36.17% sensitisation and higher IgE values in the group aged 6–10 years (12.46±10.42 kUA/L). In fact, all patients sensitised to olive recognise *Ole e 1* and *Ole e 9*, while only one patient also recognises *Ole e 7*.

In addition, sensitisation to *Phl p 1* (33.3±9.47 kUA/L), from the grass group, was observed in 19.15% of patients, as well as to *Lol p 1* (0.98±2.72 kUA/L). Other grass allergens, such as *Phl p 2* (0.34±1.76 kUA/L), *Phl p 5* (1.73±7.91 kUA/L), and *Phl p 6* (0.24±1.29 kUA/L), showed lower frequencies of sensitisation (6.38% each). Even *Phl p 12* was not recognised by any of the study patients.

Furthermore, sensitisation to *Cup a 1* is low in all groups, with a prevalence of 19.15%, and low IgE levels (0.97±3.28 kUA/L). Additionally, *Pla a* (Platanus acerifolia) shows a low prevalence, with slight sensitisation to *Pla a 3* (0.26±0.95 kUA/L; 10.6%).

In general, sensitisation to pollens is more frequent in children aged 6–10 years, suggesting higher exposure during this stage, while IgE levels tend to stabilise in adolescents aged 11–15 years.

Epithelia sensitisation

Animal epithelia were also recognised in a significant percentage of patients. *Fel d 1* had a mean sIgE of 2.93±9.03 kUA/L and a sensitisation frequency of 27.66%. However, *Fel d 2* was not recognised by any of the studied patients. On the other hand, *Can f 1* (1.68±7.28 kUA/L) showed a sensitisation frequency of 17.02%, making it the most prevalent allergen associated with dog allergy in this population. A variable pattern of dog epithelium allergen recognition was observed, as only five patients were monosensitised to a single component, while the rest exhibited a more complex sensitisation pattern with different combinations of recognised dog allergen components.

Furthermore, in Figure 2A, older patients (11–15 years) showed higher reactivity to epithelial allergens than the other age groups. This is also reflected in Figure 2C, where the 11–15 age group shows the highest IgE values to these epithelia.

Fungi sensitisation

The prevalence of fungal sensitisation was relatively low in this cohort. According to Table 2, *Alt a 1* was identified as the most prevalent allergen, with a sensitisation frequency of 21.28% and a mean of 4.58±12.14 kUA/L. Only one patient recognised *Alt a 6* (0.09±0.59 kUA/L). Figure 2A illustrates that reactivity to *Alt a 1* was predominantly observed in the youngest patients (0–5 years), and it subsequently exhibited a decline. This trend was further substantiated by Figures 2B and 2C, which revealed elevated IgE values in the youngest group compared to the others.

Discussion

The present study analysed a sample of 47 paediatric patients from the Mediterranean area with the objective of establishing a molecular pattern of sensitisation, determining the prevalence of each allergenic component of different aeroallergens, and exploring a potential influence of age on these data.

The implementation of a comprehensive allergen panel enables the advancement of sensitisation profiling within our population, facilitating an increasingly accurate evaluation. The possibility of performing the assessment from birth generates knowledge about the initial stages of allergic disease, allowing the identification of the initiating factors and molecules that are related to the development of different diseases. This has significant implications for the diagnosis and treatment of allergic diseases in children and reinforces our observation that molecular diagnostics are crucial for a model of precision medicine.[5,6]

A large part of the sample had moderate or severe rhinitis. Moreover, just over half of the patients also had asthma, highlighting the frequent coexistence of asthma with allergic rhinitis. Most cases of asthma were moderate, which is consistent with studies in similar populations indicating that moderate asthma is more common in children with allergic sensitisation.[10]

Our results indicate a high prevalence of sensitisation to house dust mites, pollen, and epithelia among children in the Mediterranean region, consistent with previous studies conducted in similar populations.[1] Furthermore, we observed that polysensitisation is a common phenomenon in this population, with notable overlaps between sensitisation to mites, pollen, and epithelia (21.3%).

Regarding dust mites, where the sample shows a greater number of results, we can draw a greater number of associations and conclusions. Although the Dermatophagoides group 2 (Der p 2 and Der f 2) has the highest IgE levels,

Table 2 Descriptive statistics of allergen-specific sIgE levels in a sample of 47 patients, including the mean and standard deviation of sIgE (kUA/L), as well as the number and frequency of recognition for each allergen.

Allergen	Mean sigE (m ± SD)	N=47 (≥0.35kU/L)	N=47(%) (≥0.35kU/L)	Allergen	Mean sigE (m ± SD)	N=47 (≥0.35kU/L)	N=47(%) (≥0.35kU/L)	Allergen	Mean sigE (m ± SD)	N=47 (≥0.35kU/L)	N=47(%) (≥0.35kU/L)
Der p 1	7.25±13.01	20	42.6	Cup a 1	0.97±3.28	9	19.1	Alt a 1	4.85±12.14	10	21.3
Der p 2	17.10±20.72	24	51.1	Pla a 1	0.00±0.00	0	0.0	Alt a 6	0.09±0.60	1	2.1
Der p 5	5.57±11.73	12	25.5	Pla a 2	0.00±0.00	0	0.0	Fel d 1	2.93±9.03	13	27.7
Der p 7	2.72±7.76	7	14.9	Pla a 3	0.26±0.95	5	10.6	Fel d 2	0.01±0.06	0	0.0
Der p 10	1.13±7.37	4	8.5	Ole e 1	8.93±16.29	17	36.2	Fel d 4	0.30±1.45	2	4.3
Der p 11	0.00±0.00	0	0.0	Ole e 7	0.02±0.11	1	2.1	Fel d 7	0.29±1.40	4	8.5
Der p 20	0.92±4.65	3	6.4	Ole e 9	7.59±14.83	17	36.2	Can f 1	1.68±7.28	8	17.0
Der p 21	3.31±10.61	8	12.8	Phl p 1	3.33±9.47	9	19.1	Can f 2	1.22±0.66	4	8.5
Der p 23	6.77±11.66	28	59.6	Phl p 12	0.00±0.00	0	0	Can f 3	0.07±0.35	2	4.3
Der f 1	2.56±5.04	18	38.3	Phl p 2	0.35±1.78	3	6.4	Can f 4	1.87±8.14	3	6.4
Der f 2	16.78±21.06	24	51.1	Phl p 5	1.73±7.91	3	6.4	Can f 5	1.29±5.20	5	10.6
Blo t 5	1.17±4.76	4	8.5	Phl p 6	0.24±1.29	3	6.4	Can f 6	1.23±0.78	3	6.4
Blo t 10	1.16±7.33	4	8.5	Phl p 7	0.01±1.1	1	2.1				
Blo t 21	0.20±1.18	2	4.3	Lol p 1	1.00±2.74	9	19.1				
Gly d 2	0.43±1.20	6	12.8	Sal k 1	1.21±4.94	5	10.6				
Lep d 2	0.08±0.28	3	6.4	Par j 2	1.27±6.28	4	8.5				
Tyr p 2	0.07±0.42	2	4.3								

showing its serodominance, Der p 23 is the most recognised allergen, a fact that is already known in other regions of Spain.[4,11,12] This is of great interest from a therapeutic point of view, as some studies have established sensitisation to this allergen as a biomarker of non-response to immunotherapy. However, further studies are required to determine whether this phenomenon is consistent.[13] The presence of sensitisation to Der p 23, as well as to group 1 (Der p 1 and Der f 1), has been linked to the development of severe asthma in individuals sensitised to dust mites. This is a particularly relevant observation given the age of our patients, which strengthens and supports this association that manifests at an early age. Moreover, the evaluation of the largest possible number of allergens in a patient sensitised to dust mites seems to be decisive for establishing a correct diagnosis, as the presence of group 5, 20, and 21 allergens at an early age reveals their importance.[14] This type of diagnosis goes far beyond the simple prick and IgE tests for the whole allergen, a standard diagnostic procedure that could be inaccurate and incomplete for patients in our population who are sensitised to dust mites.

It is ground-breaking that the presence of asthma in individuals with rhinoconjunctivitis is associated with a higher number of recognised allergens, including Der p 5, Der p 7, Der p 20, and Der p 21. This finding has not been previously observed, probably due to the utilisation of alternative platforms to ALEX2. The latter encompasses the full range of allergens available on the platform, enabling the investigation of allergens thought to be of little relevance. This has led to the identification of potential associations that were previously undocumented.

The analysis of pollen sensitisation in this paediatric population reveals several key trends, with the most frequently recognised pollen allergens coming from the Oleaceae, Poaceae, Cupressaceae, and Platanaceae families. Olive tree allergens, particularly Ole e 1, showed high recognition across all age groups, especially in children aged 6–10 years, and were often accompanied by Ole e 9 sensitisation. In the Poaceae family (grasses), Phl p 1 showed the highest sensitisation rate and significantly elevated IgE, particularly in the 6–10 age group. Other grass allergens showed much lower sensitisation rates. Cupressaceae (Cup a 1) and Platanus acerifolia (Pla a 3) allergens exhibited low sensitisation rates and IgE levels.

For some allergens, one molecule or several molecules can act as initiators, as has been shown in several studies in certain populations.[15,16] This is the case for Phl p 1, recognised in this study in all patients sensitised to grasses, and Ole e 1 in those sensitised to olive. Both are markers of genuine sensitisation to these pollens, just like Cup a 1. On the other hand, we found no relationship between the presence of these allergens and the occurrence of the different atopic diseases. This is probably due to the small sample size, as associations between the presence of asthma in patients who recognise the major allergens of these pollens have been well described in Mediterranean populations.[17]

Overall, the data suggest that pollen sensitisation is more common in children aged 6–10 years, likely due to increased environmental exposure during this period.[18] However, IgE levels tend to stabilise over the years, indicating that initial sensitisation may occur earlier in childhood, with subsequent exposure leading to consistent IgE production.[19] This age-dependent pattern of sensitisation may have important implications for the timing of diagnostic testing and the initiation of allergen-specific immunotherapy in paediatric populations.

The results of this study highlight the significant role of animal epithelial allergens in paediatric sensitisation, particularly regarding cat and dog allergens. Fel d 1, the primary cat allergen, was recognised in a substantial portion of the population. However, no patient demonstrated sensitisation to Fel d 2, suggesting that Fel d 1 remains the dominant cat allergen in this population. In contrast, Can f 1 exhibited a lower frequency of sensitisation and sIgE levels, despite being the most prevalent canine allergen in this study. Interestingly, dog epithelial sensitisation exhibited a more variable pattern, with five patients showing monosensitisation to a single component, while the remainder demonstrated a more complex sensitisation profile, recognising multiple dog allergens. This complexity suggests potential differences in the underlying immunological mechanisms driving sensitisation to dog epithelia. Furthermore, a notable age-related pattern was observed, with older patients (11–15 years) showing higher reactivity to epithelial allergens. This trend may indicate a progressive increase in epithelial allergen sensitisation with age, possibly due to cumulative exposure over time or evolving immune responses in older children. This observation is consistent with previous findings suggesting that epithelial sensitisation may develop or intensify later in childhood, reinforcing the need for age-specific considerations in the diagnosis and management of animal-related allergies.[18]

Concerning fungi, sensitisation to Alternaria aligns with similar research conducted in Spain.[20] Although the Valencian Community is not particularly concerned with sensitisation to this fungus, the presence of antibodies against Alt a 1 in children under 5 years of age is noteworthy, indicating early sensitisation in the studied population. However, the number of sensitised patients decreases with age, a phenomenon previously documented in Spain.[21] Future studies involving larger cohorts are required to confirm this trend.

It is also important to acknowledge the limitations of the study. One such limitation is the difficulty in recruiting a representative sample from the 0–5 years age group, as the prevalence of allergic sensitisation is lower in this age range compared to older groups. This is due to the fact that many children have not yet manifested allergic symptoms at such an early age. It is worth noting that the age of allergy onset may be influenced by geographical location, as different environmental settings and allergen prevalence vary across regions. Areas with high exposure to aeroallergens, such as dust mites, may accelerate the onset of epithelial sensitisation in young children, in contrast to other regions where these allergens are less prevalent. This regional variability may limit the generalisability of our findings to other child populations. Therefore, similar studies conducted in different geographical regions are necessary.

Conclusions

In conclusion, the findings of this study provide further evidence of the complex nature of allergic sensitisation, particularly in paediatric populations, and underscore the importance of understanding both the environmental and

immunological factors that contribute to allergic disease development. Our results highlight the high prevalence of sensitisation to house dust mites, pollens, and animal epithelia in this Mediterranean paediatric population, with notable recognition patterns for specific molecular allergens such as Der p 23, Ole e 1, and Can f 1. Additionally, we observed a predominant pattern of polysensitisation, with mites being the most frequently recognised allergenic source.

The distribution of sensitisation across different age groups suggests that both exposure to and immune response to allergens evolve over time, which has significant implications for early diagnosis and intervention strategies. These findings emphasise the relevance of precision medicine in allergy management, particularly in informing the selection of allergen immunotherapy. Future research involving larger cohorts and longitudinal follow-up will be crucial to further clarify the clinical impact of these sensitisation patterns and to optimise personalised treatment approaches for allergic diseases in children.

Authors Contributions

All authors contributed equally to this article.

Conflicts of Interest

T.G.D and F.P. were employed by the company Inmunotek; S.L. The remaining authors declare that the research was conducted in th absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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