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CASE REPORT

The Precision Allergy Molecular Diagnosis (PAMD@) in Monitoring the Atopic March in a Child with a Primary Food Allergy: Case Report

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Abstract: The case of a 9-month-old boy with an initial diagnosis of atopic dermatitis and confirmed allergy to hen's egg, cow's milk allergens with episodes of anaphylaxis who developed birch allergy whilst under observation with asthma symptoms was presented. The precision allergy molecular diagnosis (PAMD @) allowed for individualisation of dietary recommendations and observing the early progression of food sensitisation to the main birch molecule. The presented identification of major allergic molecules with PAMD@ in the preclinical phase of asthma contributes to the discussion related to early specific immunotherapy to suppress molecular spread and allergic march. However, more research is needed to verify this hypothesis.

Keywords: atopic march, allergy, anaphylaxis, sIgE, PAMD@, multiplex molecular tests

Introduction

Food allergy (FA) is often the first step of other atopic manifestations later in life, and this phenomenon is commonly named the atopic march.[1] It has been proposed that the precision allergy molecular diagnosis (PAMD@) could help identify some risks for the atopic child and predict the development of the atopic march.[2]

The article presents a case of a patient with an initially diagnosed FA manifested as atopic dermatitis (AD) and anaphylaxis, which evolved into childhood asthma. The patient's diagnostic process was based on PAMD@ and allergen challenge.

Clinical Case

In September 2019, a 9-month-old boy with AD and anaphylaxis who ate scrambled eggs on clarified butter after eating for the first time in his life was admitted to the Central Clinical Hospital of the Ministry of Inferior and Administration in Warsaw.

Paediatric history: the child was born by caesarean section at 38 Hbd, 10 Apgar score, the father has a pollen allergy and bronchial asthma, the mother is allergic to nickel, and one older brother is without allergy. The boy was breastfed for 9 months, and at the age of 6 months, the diet was extended with fruits, vegetables and meat. A month later, emesis after eating the cooked yolk, ear oedema and hives after homogenised cheese were observed. Symptoms regressed after

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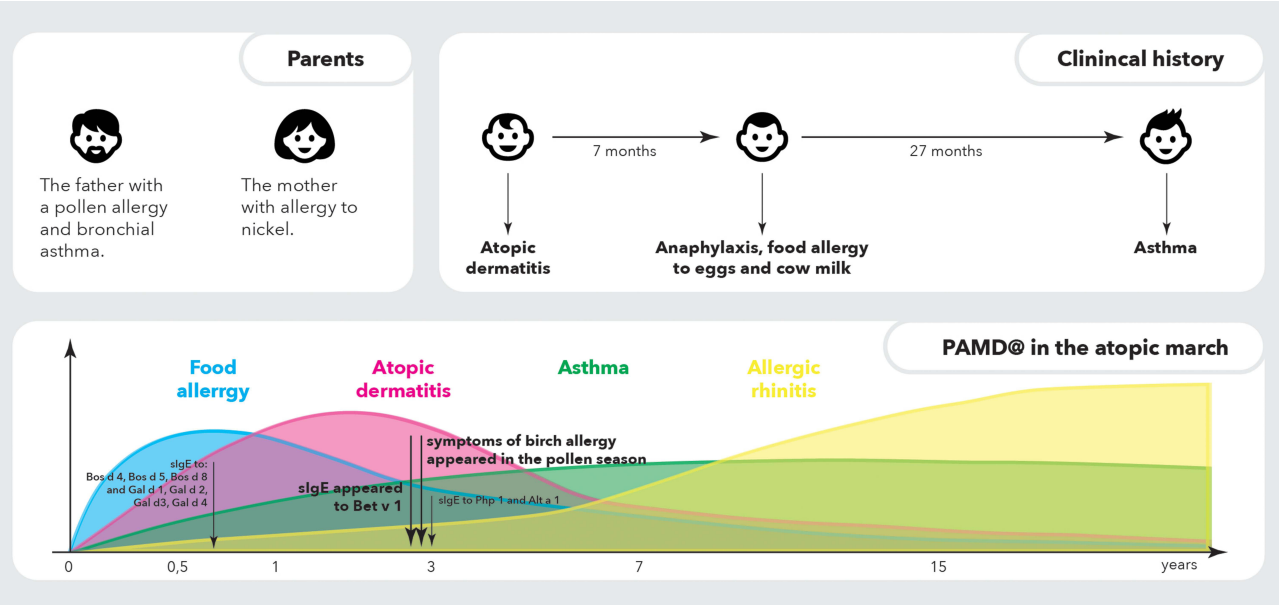
Graphical Abstract



administering cetirizine (5 mg/day). Laboratory tests showed eosinophilia in peripheral blood (8.6%), total IgE <20 kU/L and specific IgE (sIgE) to cow's milk, hen's egg, soybean, peanut and potato (Table 1).

Recommendations included an elimination diet without milk and eggs for the mother and child, further breastfeeding, feeding with amino acid formula, taking cetirizine as needed and avoiding soybean and nuts. The child was equipped with an anti-shock kit.

During 30 months of observation, dietary recommendations were followed, and the severity of skin lesions reduced (↓SCORAD from 33 to 9 points) without episodes of anaphylaxis. An attempt to discontinue cetirizine, despite the use of a restrictive elimination diet, resulted in the appearance of allergic symptoms. In 2019–2020, the patient had three bronchitis episodes with wheezing, treated with antibiotics. In 2021, in the period of birch pollination, the patient had bronchitis without fever, with preceding symptoms of acute conjunctivitis and rhinitis. He was treated with inhaled fluticasone preparation via low volume inhalation chamber, fenoterol with ipratropium bromide as nebulisation, nasal preparation of mometasone furoate and intraconjunctival hydrocortisone with a good clinical effect. In April 2022, the patient developed symptoms of full-blown asthma (cough with shortness of breath). Inhalation treatment with fluticasone propionate with salmeterol was intensified, treatment with oral antihistamine and nasal steroid was continued, and the patient's condition improved.

The first single-blind, placebo-controlled challenge with baked milk after 12 months of elimination diet was positive (after eating 1/2 of a muffin), as was the second one after 18 months (after eating 1/12 of a muffin). A challenge with a chicken egg after 19 months of the elimination diet was also positive.

The PAMD@ was performed prior to the milk challenge (FABER multiplex; 11/2019) and then repeated twice (ALEX multiplex; 02/2021, 01/2022) (Table 2). ALEX multiplex (02/2021) done after 14 months of FABER test showed persisted positivity against hen's egg extract and components (ovomucoid, ovalbumin, ovotransferrin), cow's milk extract and components (beta-lactoglobulin, casein) and the milk of other ungulates. sIgE to birch (Bet v 1) was 0.27 kU/L, but it was still below the cut-off (0.35kU/L). Re-performed ALEX test (01/2022) presented new sensitisation to grass and *Alternaria alternata*, and progression of sensitisation to Bet v 1 (2.33 kU/L) (Table 2). Due to increased sensitisation to milk components, including casein, another milk challenge was not attempted, and the elimination diet without milk, eggs and nuts was maintained.

We have obtained the signed consent from the patient's parents and the hospital to publish the case details.

Table 1 Study of Specific IgE in 29-Month Lasting Follow-Up

Allergen Component		Euroline Pediatric Profile*	Polycheck Egg Components **	FABER***	ALEX****	ALEX****
Unit of measure		kU/L	kU/L	FIU/mL	kU/L	kU/L
Date of execution		09/2019	10/2019	11/2019	02/2021	01/2022
Time since introducing an elimination diet		Without an elimination diet		After 2 months	After 17 months	After 28 months
Age of the patient in months		9	10	11	26	37
Food allergens	Alpha-lactalbumin (Bos d 4)	**1.70**		**0.54 (n)**	≤0.1 (n)	≤0.10 (n)
	Beta-lactoglobulin (Bos d 5)	**36.00**		**0.81 (n)**	0.32 (n)	**1.10 (n)**
	Casein (Bos d 8)	**16.80**		**1.62 (n)**	**1.15 (n)**	**4.52 (n)**
	Ovomucoid (Gal d 1)		**3.10 (n)**	**4.29 (n)**	**2.74 (n)**	**2.39 (n)**
	Ovalbumin (Gal d 2)		**3.50 (n)**	<0.01 (n)	**3.66 (n)**	**0.79 (n)**
	Ovotransferrin (Gal d 3)		**5.80 (n)**	**0.81 (n)**	**0.66 (n)**	**0.43 (n)**
	Lysozyme (Gal d 4)		**23.00 (n)**	<0.01 (n)	≤0.10 (n)	≤0.10 (n)
Inhalation allergens	Birch (Bet v 1)			<0.01 (r)	0.27 (r)	**2.33 (r)**
	Timothy (Phl p 1)			<0.01 (r)	≤0.10 (r)	**1.51 (r)**
	Alternaria alternata (Alt a 1)			<0.01 (r)	≤0.10 (r)	**5.35 (r)**

Notes: (r) – recombinant (n) – natural; filling colour grey – no data, due to non-performance of the measurement at a given time or no such measurement on a given test. *The results were obtained with the use of a multi-parameter Euroline immunoassay (Euroimmun, PerkinElmer Germany Diagnostics GmbH containing 27 allergens). Positive result ≥ 0.35 kU/L. **The results were obtained with the use of multi-parameter Polycheck assay (Biocheck GmBH, Germany). Positive result ≥0.35 kU/L. ***Multi-parameter FABER immunoassay (CAAM, Rome, Italy) - negative result <0.01 FIU/mL, borderline >0.01/<0.30 FIU/mL, positive ≥0.30 FIU/mL. ****Multi-parameter ALEX immunoassay (MacroArray Diagnostics, Vienna, Austria) – negative or borderline result <0.3 kU/L, positive result ≥0.3 kU/L. Bold numbers – positive result (result ≥0.35 kU/L). Underlined numbers – borderline result (result between 0.1 kU/L and <0.35 kU/L).

Table 2 Assessment of Asthma Predictive Index in the Presented Patient

Assessed Criteria*	Patient's Signs and Symptoms
Major Criteria	
Asthma in parents	Yes
Atopic eczema	Yes
Minor Criteria	
Allergic rhinitis	Yes
Wheezing without infection	Yes
Peripheral eosinophilia >4%	Yes

Notes: *The criteria for the diagnosis of asthma according to Rodríguez JA, Holberg CJ, Wright AL and Martinez FD. showed in article A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med*. 2000; 162: 1403–1406.[3]

Discussion

The described case shows a typical route of an allergy march from FA manifested as AD to inhalation allergy and asthma. The reported case presented several risk factors for the classic atopic march: AD in infancy, atopy in family, male gender and primary sensitisation to many food allergens.[1] The Asthma Predictive Index assessment[3] confirmed a high

probability of asthma development: the patients met two major criteria (AD, asthma in the father) and three minor criteria (allergic rhinitis, peripheral eosinophilia, wheezing without infection) (Table 2). After considering the patient's age, the diagnosis of asthma was carried out in accordance with the applicable guidelines of COMPAS GP (ReCOMmendations for management of Preschool ASthma for General Practitioners).[4]

In the presented case, dietary treatment was applied after identifying food allergens and the food challenges with baked cow's milk and hen's eggs that were positively correlated with the presence of sIgE in the milk and egg molecules responsible for the persistent allergy. In addition, we observed that the concentration of sIgE to Bet v 1 increased from 0.27 kU/L to 2.33 kU/L. Since the boy showed symptoms at the time of birch pollination, we were able to recognise allergy to birch when the concentration of sIgE to Bet v1 was at the level of 0.27 kU/L. It is believed that the cut-off for positive results is the value of 0.35 kU/L, but it is necessary to underline that the limit of 0.35 kU/L for positive serological tests established by Johansson in the 1970s resulted from the sensitivity of diagnostic methods used at that time. A change in standard values for specific IgE has been proposed recently, and the cut-off value for sIgE at the level of 0.1 kU/L has been suggested.[5] In our patient, clinical observations of evident allergy to birch were confirmed by the result of a re-performed ALEX test, which showed sIgE to Bet v 1 at the level of 2.33 kU/L. Thus, in the presented case, low sIgE values (<0.35 kU/L) to allergen components may be significant with regard to future allergies. Thanks to the possibility of determining sIgE to allergen molecules, we observed the process of conversion from asymptomatic allergy to full clinical manifestation of birch allergy.

There are not many observations of molecular spread in FA and inhalation allergy. One of such reports was presented by Matricardi et al, who assessed the dynamics of specific component sensitisation of Phleum pratense timothy allergen[6] in 7 years in a boy who was initially allergic only to Phl p 1 at 3 years of age. Then, at the age of 6, the patient was already allergic to Phl p 1 and Phl p 2, and at the age of 10, to molecules Phl p 4, Phl p 5, Phl p 6 and Phl p 11. The authors wondered whether the introduction of allergen-specific immunotherapy could inhibit or limit the process of allergen spreading. The present case is another one that allows us to think about the need to verify the effectiveness of such early allergen immunotherapy in the context of inhibiting the allergic march.[6]

Therefore, the presented case is important as one of the few described in the literature that contributes to considering the optimal timing of the introduction of immunotherapy. It also presents the benefits of PAMD@ in dietary treatment, predicting the risk of anaphylaxis, and assisting in making decisions about provoking selected allergens.

Limitations

During the patient's diagnosis, various diagnostic methods were used, which were dictated by their current availability (eg, since 2021, the possibility to measure sIgE with FABER has been abolished in Poland and worldwide). Different tests make it impossible to compare the obtained sIgE values. In contrast to the semi-quantitative FABER and Euroline tests, Polycheck and ALEX are quantitative tests. In addition, sIgE measurement was performed at different stages of treatment: the FABER test was done on a dairy-free and egg-free diet, and the ALEX test when the elimination of nuts and legumes was added, which could have influenced the obtained sIgE results for these allergens. Thus, the comparison of sIgE values against allergen components (Table 1) is only indicative.

Conclusion

In conclusion, the use of PAMD@ in clinically manifested FA allowed for individualisation of dietary recommendations and revealed an early progression of sensitisation to the main molecule of birch.

The identification of major allergic molecules with PAMD@ in the early preclinical phase of the disease contributes to the discussion related to early specific immunotherapy to suppress molecular spread and allergic march. However, more research is needed to verify this hypothesis.

Disclosure

The authors report no conflicts of interest in this work.

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