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Letter to the Editor

Mal d 1 and Bet v 1 sensitization pattern in children with Pollen Food Syndrome

Dear Editor,

The major allergen for the *Betulaceae* family is Bet v 1, a pathogenesis-related protein (PR)-10, that shares a molecular homology with pollens of several plants, including hazel, hornbeam, and hop-hornbeam.[1] Pollen Food Syndrome (PFS) is a common allergic disorder sustained by a pollen-fruit cross-reaction. Oral allergy syndrome (OAS) is the most common clinical representation of PFS and is defined by the occurrence of itching and tingling of the lips, mouth, and throat immediately after eating some fruits and vegetables. The most frequent OAS occurs in Bet v 1-sensitized patients when eating fruits from the *Rosaceae* family, mainly apple.[2] Apple OAS depends on the molecular homology between Bet v 1 and the Bet v 1-homologous Mal d 1, the major allergen of apple belonging to PR-10 family.[2] Recently, it has been reported that adult patients with *Betulaceae* allergy and with OAS had higher serum IgE levels to Bet v 1 than patients without OAS.[3] Therefore, this study aimed to verify the hypothesis that also children with Bet v 1-sensitization and apple allergy have a different molecular pattern in comparison with Bet v 1-sensitized children without apple allergy.

This retrospective study enrolled a series of consecutive children suffering from respiratory allergy with Bet v 1 sensitization visited to define appropriate treatment. We analyzed the findings of serum allergen-specific IgE assessed by the ISAC method as previously reported.[4] OAS was diagnosed as previously defined according to validated criteria.[5] The Review Board of the Istituto Giannina Gaslini approved the procedure. The patients' parents gave a written informed consent.

Serum IgE were measured by ISAC test according to previous study Bet v 1 and Mal d 1 allergen-specific IgE levels are reported as median with lower and upper quartiles in parentheses and compared using the Kruskal Wallis test followed by Dunn's Multiple Comparison Test (if three groups were compared) or using the Mann U Whitney test (if two groups were compared). Frequencies were compared by the Chi-square of Fisher's Exact test (as appropriate). All the tests were two-sided and a p value < 0.05 was considered as statistically significant.

One-hundred and thirty-seven patients were enrolled: all of them were sensitized to Bet v 1 and 110 were also sensitized to Mal d 1. History of allergic disease is reported in Table 1. Forty-two reported OAS after apple ingestion, all of them were sensitized to Mal d 1. Dividing the study population on the basis of Mal d 1 sensitization and OAS, we had 68 patients sensitized to Mal d 1 without OAS, 42 patients sensitized to Mal d 1 with OAS, 27 patients not sensitized to Mal d 1 without OAS and no patient not sensitized to Mal d 1 with OAS. Age was not different among the different groups ($p = 0.29$). Male gender was significantly more frequent in patients without OAS (Table 1). History of allergic disorders was superimposable between groups ($p = 0.68$). Patients with *Betulaceae* allergy and with co-sensitization to Mal d 1 reported OAS after apple ingestion more frequently as compared to those without co-sensitization to Mal d 1: 38.2% vs. 0%, respectively ($p = 0.0001$). Mal d 1-allergen specific IgE levels were double in patients with OAS as compared to those without OAS ($p = 0.034$) (Table 1). No statistically significant difference in Bet v 2 or in Pru p 3 levels was found among the different groups ($p = 0.46$). On the basis of this result, we evaluated the best cut-off Mal d 1 levels able to discriminate between patients with or without OAS. On the basis of the Receiver Operating Characteristic (ROC) curve analysis, we identified 5.3 ISU as the optimal cutoff value of Mal d 1-specific IgE, but the performance was not very good: the value of the area under the ROC curve (AUC) corresponds a level of performance of little more than that of chance being 0.62 [95% Confidence interval (95%CI): 0.52–0.71]. Also, sensitivity [69.0 (52.9–82.4)], specificity [63.2 (50.7–74.6)], positive likelihood ratio (1.88) and negative likelihood ratio (0.49) were moderated (Fig. 1A). Bet v 1- allergen specific IgE levels were compared in the three groups of patients. Independently from OAS, patients sensitized to Mal d 1 had significantly higher Bet v 1-allergen specific IgE levels as compared to those not sensitized to Mal d 1 without OAS being 19.55 (10.60–42.35) ISU in Mal d 1- sensitized patients with OAS ($p < 0.001$, vs patients not sensitized to Mal d 1 and without OAS), 13.35 (3.05–24.30) ISU in Mal d 1-sensitized patients without OAS ($p < 0.001$, vs patients not sensitized to Mal d 1 and without OAS), and 0.80 (0.55–2.80) ISU in patients not sensitized to Mal d 1 and without OAS (Kruskal–Wallis test: $p < 0.001$). We also found that Bet v 1-allergen specific IgE levels were significantly higher in patients with OAS than in those without OAS ($p < 0.001$) (Table 1). On the basis of the ROC curve analysis, we identified 8.2 ISU as the optimal cutoff value of Bet v 1-specific IgE able to discriminate between patients with or without OAS. The performance was good being the area under the ROC curve (AUC) corresponding to an acceptable discrimination of 0.72 [95% Confidence interval (95% CI): 0.63–0.79] (Fig. 1B). A very strong correlation was found between Bet v 1 and Mal d 1 allergen specific IgE levels ($r = 0.84$, $p < 0.0001$).

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Table 1
Demographics and Allergen specific IgE levels towards Mal d1 1 or Bet v 1 in patients with or without OAS.

	OAS+			OAS−		
	Whole population (No. 42)	Mal d 1 − positive (No. 42)	Mal d 1 − negative (No. 0)	Whole population (No. 95)	Mal d 1 − positive (No. 68)	Mal d 1 − negative (No. 27)
Age [mean (SD)]	9.88 (3.31)	9.88 (3.31)	–	8.91 (3.55)	8.79 (3.38)	9.21 (4.00)
Gender	18 m, 24f***	18 m, 24f	–	76 m, 19f	53 m, 15f**	23 m, 4f*
Atopic dermatitis	8	8	–	22	15	7
Allergic rhinitis	42	8		95	68 27	
Allergic asthma	13	8	–	31	22	9
Allergen specific IgE levels (ISU) [median (LQ-UQ)]						
Mal d 1 (No. 110)	7.25 (3.00–16.30)	7.25 (3.00–16.30)	–	3.75 (1.25–12.55)	–	–
Bet v 1 (No. 137)	19.55*** (10.60–42.35)	19.55† (10.60–42.35)	–	4.70 (1.15–19.90)	13.35† (3.05–24.30)	0.80 (0.55–2.80)
Bet v 2 (No. 14)	5.10 (3.10–11.75)	5.10 (3.10–11.75)	–	0.90 (0.85–11.10)	0.90 (0.30–10.0)‡	3.10 (0.80–12.20) ^
Pru p 3 (No. 44)	1.00 (0.50–2.20)	1.00 (0.50–2.20)	–	1.30 (0.65–3.20)	1.30 (0.80–3.50)	0.80 (0.45–7.40)

*p < 0.01, vs patients with OAS.
**p < 0.001, vs patients with OAS.
***p < 0.001, vs patients without OAS.
† vs patients not sensitized to Mal d 1 and without OAS (post hoc test).
‡ min–max.

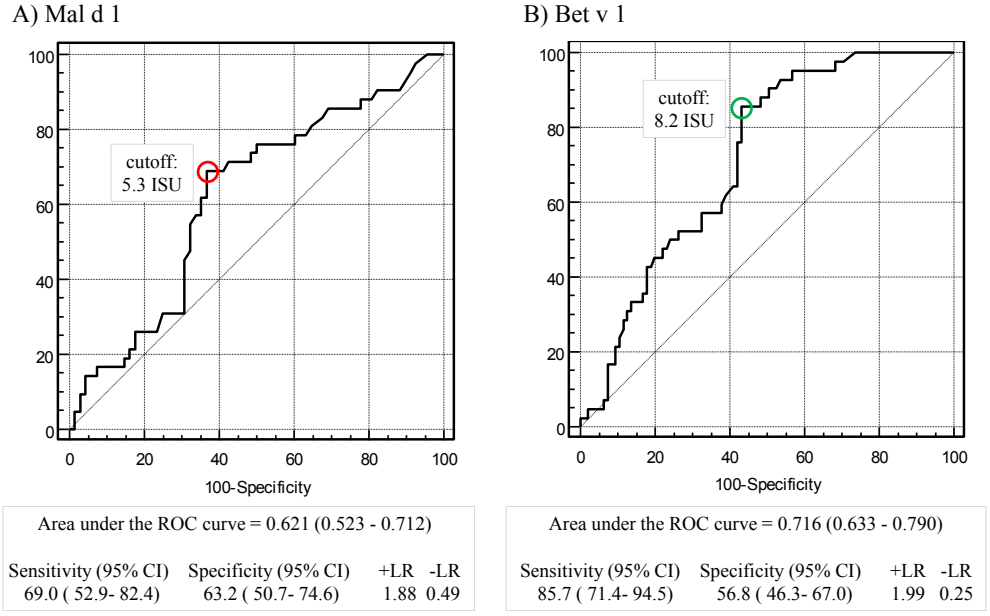

Fig. 1. Receiver Operating Characteristic (ROC) curve analysis to calculate the best cutoff of Mal d 1 allergen-specific **(A)** or Bet v 1 **(B)** allergen-specific IgE levels able to discriminate between patients with or without OAS.

Allergy to *Betulaceae* pollen allergens is common in our geographic area and OAS may be frequently associated.[6] In addition, it was demonstrated that micro-array platform is a reliable tool for diagnosing pollen allergy[7]; serum IgE assessment may be also a reliable tool for defining true allergy, for predicting response to allergen immunotherapy and severe reaction to oral immunotherapy, and may be related to symptom severity.[8,9] The current study confirmed that the serum IgE level to both Mal d 1 and Bet v 1 could be reliable biomarker to define apple allergy in children sensitized to Bet v 1. Moreover, these findings are consistent with previous outcomes obtained in Japanese allergic patients using component-resolved diagnosis in birch pollen-related OAS.[10]

In conclusion, high serum IgE to Bet v1 and to Mal d 1 levels may be reasonably predictive of true apple allergy in clinical practice.

Conflict of interest
The authors have no conflict of interest to declare.

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References

1. Brier S, Le Mignon M, Jain K, Lebrun C, Peurois F, Kellenberger C, et al. Characterization of epitope specificities of reference antibodies used for the quantification of the birch pollen allergen Bet v 1. *Allergy* 2018;**73**:1032–40.
2. Webber CM, England RW. Oral allergy syndrome: a clinical, diagnostic, and therapeutic challenge. *Ann Allergy Asthma Immunol* 2010;**104**:101–8.

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3. Ciprandi G, Comite P, Ferrero F, Bignardi D, Minale P, Voltolini S, et al. Birch allergy and oral allergy syndrome: the practical relevance of serum immunoglobulin E to Bet v 1. *Allergy Asthma Proc* 2016;**37**:43–9.
4. Tosca MA, Silvestri M, Olcese R, Pistorio A, Rossi GA, Ciprandi G. The impact of age on serum allergen-specific IgE to inhaled molecular components. *Allergol Immunopathol (Madr)* 2017;**45**:265–71.
5. Katelaris CH. Food allergy and oral allergy or pollen-food syndrome. *Curr Opin Allergy Clin Immunol* 2010;**10**:246–51.
6. Negrini AC, Negrini S, Giunta V, Quaglini S, Ciprandi G. Thirty-year survey on airborne pollen concentrations in Genoa (Italy): relationship with sensitizations, meteorological data, and air pollution. *Am J Rhinol Allergy* 2011;**25**:232–41.
7. Williams P, Önell A, Baldracchini F, Hui V, Jolles S, El-Shanawany T. Evaluation of a novel automated allergy microarray platform compared with three other allergy testmethods. *Clin Exp Immunol* 2016;**184**:1–10.
8. Reier-Nielsen T, Michelsen MM, Lodrup Carlsen KC, Carlsen KH, Mowinckel P, Nygaard UC, et al. Predicting reactivity threshold in children with anaphylaxis to peanut. *Clin Exp Allergy* 2018;**48**:415–23.
9. Corsico AG, De Amici M, Ronzoni V, Giunta V, Mennitti MC, Viscardi A, et al. Allergen-specific immunoglobulin E and allergic rhinitis severity. *Allergy Rhinol (Providence)* 2017;**8**:1–4.
10. Shirasaki H, Yamamoto T, Abe S, Kanaizumi E, Kikuchi M, Himi T. Clinical benefit of component-resolved diagnosis in Japanese birch-allergic patients with a convincing history of apple or peach allergy. *Auris Nasus Larynx* 2017;**44**:442–6.

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