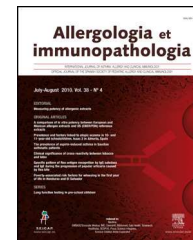




# Allergologia et immunopathologia

www.elsevier.es/ai



## RESEARCH LETTERS

### Food-dependent exercise-induced anaphylaxis (FDEIA) by nectarine in a paediatric patient with weakly positive nectarine prick-by-prick and negative specific IgE to Pru p 3

To the Editor,

Food-dependent exercise-induced anaphylaxis (FDEIA) is characterised by the onset of anaphylaxis during (or soon after) exercise preceded by ingestion of a food allergen. In FDEIA, both food allergens and exercise are independently tolerated.<sup>1</sup> This syndrome has been associated with wheat, seafood, peanut, egg, milk, vegetables and fruits.<sup>2</sup> Rosaceae fruits may also be involved. There are two major clinical patterns of allergy involved with this fruit family. One is the oral allergy syndrome (OAS) caused by sensitisation to Bet v 1 – a homologous protein in patients with birch pollens allergy – and/or caused by sensitisation to profilin.<sup>3</sup> The other one is associated with sensitisation to lipid transfer proteins (LTP), and may cause both OAS and systemic reactions – as FDEIA – and is often observed in patients living in the Mediterranean area.<sup>4</sup> We report a paediatric case of FDEIA induced by nectarine (a variety of peach), with undetectable serum specific IgE to peach LTP (Pru p 3).

A 14-year-old boy, with a history of seasonal allergic rhinitis caused by both grass and cypress pollens, experienced an episode of FDEIA during an intense exercise after eating Rosaceae fruits. In August, during a break of an athletic race, he ate two nectarines with peel and after a few minutes he started running again and immediately experienced bilateral ocular oedema, nasal obstruction and ocular and nasal itching. Before this episode, the boy was regularly eating nectarines with peel, even if he never performed physical exercises after eating this fruit. Skin prick tests (SPT) with commercial peach extract and prick-by-prick (PP) with peach (pulp and peel) were performed two weeks later, and had uncertain outcome (mean wheal diameter 2 mm). Since then, the boy no longer eats Rosaceae fruits and kept doing sports (about four times a week) without any adverse reaction.

We met the boy for the first time in October, when nectarine was not a seasonal fruit. So we were not able to

perform PP with fresh fruit at that time, and we performed PP in the next summer.

### Specific IgE detection

SPT with peach commercial extract (Lofarma, Milan, Italy, containing 40 mcg/ml LTP) was performed on two separate occasions with 10 months interval, and they showed mean wheals diameters of 2 mm. PP performed with peach fruit juice (Jolly Colombani, containing about 50% of pulp and 1% of peel) and with nectarine (pulp and peel) showed mean wheal diameters of 2 and 3 mm, respectively. Values of seric specific IgE (ImmunoCAP, Phadia, Uppsala, Sweden) scored as follows: peach=0.10 kUA/L, apple and apricot=0.00 kUA/L, cherry=0.03 kUA/L, and plum=0.01 kUA/L. Molecular allergologic test (microarray ImmunoCAP ISAC 103, Phadia, Uppsala, Sweden) resulted positive for Fel d 1 (0.17 kUA/L), Cri j 1 (0.95 kUA/L) and Cup a 1 (18.32 kUA/L). All the rest tested by ISAC resulted negative, in particular IgE specific for Pru p 3, Pru p 1, Mal d 1, Bet v 1, Bet v 2, and Bet v 4 were not detected.

### Food challenge test and exercise challenge test

We performed oral food challenge (OFC) followed by physical exercise test on two occasions. Both times, during the 24 h preceding the test, the patient had eaten as usual (pasta, meat, vegetables, bread, milk, fish, eggs) and in particular he had not been given high fat content meals or alcohol. The patient's pulmonary function tests before OFC were normal on both occasions. Our patient underwent an OFC ingesting 400 ml of peach fruit juice (Jolly Colombani, 50% of fruit, 1% of peel) and then an exercise challenge test was performed the first time (step-test, to go up one step of 30 cm 30 times per minute for 10 min) with no adverse reactions. The second OFC followed by exercise test was performed nine months later. The boy ingested two nectarines with peel and, immediately after exercise, the boy experienced a generalised adverse reaction characterised by bilateral ocular oedema and hyperaemia, ocular and nasal itching, nasal obstruction, rhinorrhoea and sneezing, throat

constriction, dyspnoea and mild wheezing (FEV1 = 87%). The blood pressure was 135/68 mmHg.

### Tryptase analysis

During the second OFC, before nectarines ingestion, our patient underwent blood tryptase analysis, which resulted negative (1.91 mcg/L, *n. v.* < 9.8 mcg/L). The test was repeated 2 h after onset of symptoms, and resulted again negative (2.39 mcg/L).

### Elisa and immunoblot analysis

The following March, ELISA and Immunoblot analysis (using peach extract, natural LPT of yellow peach and recombinant LTP as substrate) were performed on serum taken and stored during previous – the second one – OFC, and they both resulted negative. It was not possible to test nectarine natural extract, because we did not have this fruit when ELISA and Immunoblot were performed.

We presented a clinical case of sensitisation to nectarine characterised by suggestive history, positive OFC, weakly positive SPT but negative in vitro findings. We believe that this condition is unusual, because, in according to clinical signs experienced, we would have expected to find both clearly positive SPT and in vitro findings.

To find low levels of specific IgE in children with FDEIA is reported in literature.<sup>1</sup> It is also reported that there are food protein specific characteristics thought to increase their potential allergenicity (the abundance of the protein in the food, multiple and linear IgE-binding epitopes, resistance of the protein to digestion and processing, and allergen structure).<sup>5</sup> One or more of these characteristics may be enhanced or up-regulated during exercise, with the result that a state of tolerance to the food is temporarily lost, even in the presence of very low levels of specific IgE. This may justify the low values of specific serum IgE to peach and the low value of the average diameter of the wheal evoked by SPT with extracts and fresh food in our patient. Our experience suggests that, in children with FDEIA, low level of specific IgE should be considered positive. However, the absence of detectable Pru p 3 specific IgE by ISAC 103, ELISA and Immunoblot was unexpected. This suggests the possibility that these tests do not have sufficient sensitivity to detect low level of specific IgE. It is also possible that nectarine has an allergen that is not present in the yellow peach. If so, however, it remains unclear why peach PP resulted – although weakly – positive, and why the same happened with measurements of peach serum specific IgE. Moreover, the negative result of Immunoblot analysis did not allow us to further investigate the real nature of the relevant allergen protein.

We did not observe tryptase increase after the anaphylaxis experienced with nectarine OFC. In a study performed on children undergoing OFC,<sup>6</sup> high tryptase levels had an anaphylaxis sensitivity of 89% and specificity of 88%. This sensitivity level may be insufficient and explain the normal levels of tryptase of our case.

Another interesting aspect of our case is the presence of a negative OFC with peach fruit juice. LTP are more concentrated in peel than in pulp of fruit.<sup>7</sup> Tolerance to peach fruit

juice of our patient could be explained by the fact that the percentage of peel contained inside fruit juice is low.

One previous study<sup>8</sup> reported a paediatric case of FDEIA induced by Rosaceae fruits characterised by a discrepancy between positive clinical history (two episodes of FDEIA during intense exercise after eating Rosaceae fruits) and positive SPT (peach extract = 4 mm, peach pulp = 6 mm, peach peel = 2 mm), versus negative in vitro findings (Pru p 3, Pru p 1, Bet v 1, Bet v 2, and Bet v 4 scored negative). Authors suggested the possibility that the patient reacted to a different peach allergen or, alternatively, that he recognised a LTP isoform different from that in UniCAP.

Bianchi et al.<sup>8</sup> did not consider appropriate to perform an OFC followed by exercise challenge test, but our case, in which diagnosis of FDEIA by nectarine was confirmed only by OFC followed by physical exercise, shows that sensitivity of molecular diagnostic tests performed by ISAC 103 is not optimal, as also Bianchi et al. said,<sup>8</sup> and that, if clinical history is suggestive of food sensitisation, it is better to first carry out PP with natural suspected food, and eventually to perform OFC followed by exercise test.

Our conclusion is that OFC followed by exercise challenge test can be useful in children with suggestive clinical history for food sensitisation, as ISAC 103 molecular diagnostic tests sensitivity does not seem to always be optimal.

### Ethical disclosures

**Patients' data protection.** Confidentiality of data. The authors declare that no patient data appears in this article.

**Right to privacy and informed consent.** Right to privacy and informed consent. The authors declare that no patient data appears in this article.

**Protection of human subjects and animals in research.** Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

### Conflict of interest

The authors have no conflict of interest to declare.

### References

1. Toit GD. Food-dependent exercise-induced anaphylaxis in childhood. *Pediatr Allergy Immunol.* 2007;18:455–63.
2. Barg W, Medrala W, Wolanczyk-Medrala A. Exercise-induced anaphylaxis: an update on diagnosis and treatment. *Curr Allergy Asthma Rep.* 2011;11:45–51.
3. Fernández-Rivas M, Bolhaar S, González-Mancebo E, Asero R, van Leeuwen A, Bohle B, et al. Apple allergy across Europe: how allergen sensitization profiles determine the clinical expression of allergies to plant foods allergies. *J Allergy Clin Immunol.* 2006;118:481–8.
4. Asero R, Mistrello G, Roncarolo D, de Vries SC, Gautier MF, Ciurana CL, et al. Lipid transfer protein: a pan-allergen in plant-derived foods that is highly resistant to pepsin digestion. *Int Arch Allergy Immunol.* 2000;122:20–32.

5. Bannon GA. What makes a food protein an allergen? *Curr Allergy Asthma Rep.* 2004;4:43–6.
6. Lin RY, Schwartz LB, Curry A, et al. Histamine and tryptase levels in patients with acute allergic reactions: an emergency department-based study. *J Allergy Clin Immunol.* 2000;106:65–71.
7. Fernandez-Rivas M, Cuevas M. Peels of Rosaceae fruits have a higher allergenicity than pulps. *Clin Exp Allergy.* 1999;29:1239–47.
8. Bianchi A, Di Rienzo Businco A, Bondanini, Mistrello G, Carlucci A, Tripodi S. Rosaceae-associated exercise-induced anaphylaxis with positive SPT and negative IgE reactivity to Pru p3. *Eur Ann Allergy Clin Immunol.* 2011;43:122–4.

S. Miceli Sopo<sup>a,\*</sup>, S. Monaco<sup>a</sup>, V. Giorgio<sup>a</sup>, M. Calvani<sup>b</sup>, G. Mistrello<sup>c</sup>, R. Onesimo<sup>a</sup>

<sup>a</sup> *Department of Paediatrics, Catholic University, Rome, Italy*

<sup>b</sup> *Department of Paediatrics, San Camillo Hospital, Rome, Italy*

<sup>c</sup> *Lofarma SpA, Milano, Italy*

\*Corresponding author.

E-mail address: [smicelisopo@rm.unicatt.it](mailto:smicelisopo@rm.unicatt.it) (S. Miceli Sopo).

<http://dx.doi.org/10.1016/j.aller.2012.07.009>

## Fixed drug eruption due to ibuprofen with patch test positive on the residual lesion

To the Editor,

Ibuprofen is a non-steroidal anti-inflammatory drug that belongs to the propionic acid group.<sup>1</sup> Skin reactions to ibuprofen include urticaria, angio-oedema, contact dermatitis and photosensitivity. Fixed drug eruption due to ibuprofen has rarely been described.

Fixed drug eruption is characterised by sudden onset of round and/or oval, oedematous, dusky-red macules on the skin and/or mucous membranes, accompanied by burning and/or itching.<sup>2</sup>

We report a case of fixed drug eruption due to ibuprofen with tolerance to acetylsalicylic acid.

A 64-year-old man with no history of atopy or drug allergy presented one year ago with three pruritic erythematous macules on his right knee, right calf, and right flank, as well as an aphthous ulcer on the oral mucosa, a few hours after taking allopurinol (Faes Farma SA; Madrid, Spain) and ibuprofen (Kern Pharma SL; Madrid, Spain). The mucosal lesions resolved some days later without treatment, leaving hyperpigmented lesions on the affected skin measuring 4 cm in diameter. The patient had previously tolerated both drugs.

The patient was referred to our Allergy Department for further study. He reported that the previous day he had taken ibuprofen and tetrazepam (Sanofi-Synthelabo; Barcelona, Spain) for a muscular contracture. Eight hours after taking the drugs, he developed the same skin lesions, although with no aphthous ulcers on the oral mucosa. Skin sections of the right calf showed a variable dermal perivascular and bandlike lymphocytic and eosinophilic infiltrate with focal basilar vacuolopathy and post inflammatory pigmentation.

One month later, the patient underwent patch testing (upper back) with allopurinol 1% and 10%, ibuprofen 1% and 5%, and tetrazepam 1% and 10%, all in petrolatum (Nonwoven Patch test Strips Curatest®; Lohman&Rauscher International; Rangsdorf, Germany). Ibuprofen 1% and 5% were applied to the calf lesion. The results of the patch test on the residual lesion at 48 and 96 h were positive with ibuprofen 1% (++) and ibuprofen 5% (+++) (Fig. 1). The results

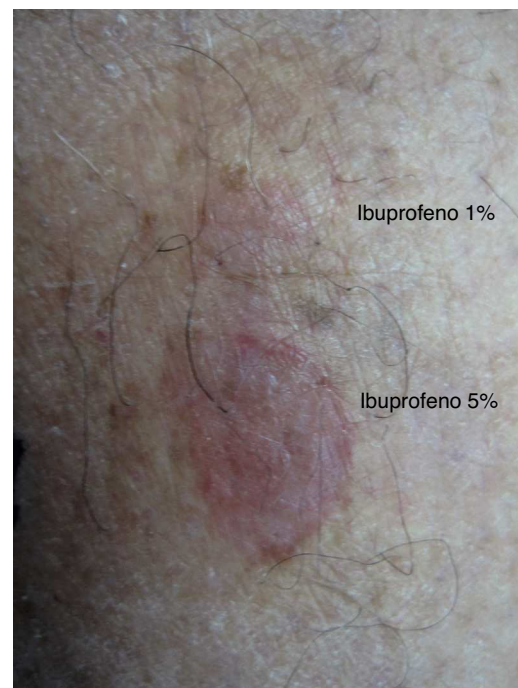
of the tests on the upper back were all negative. Patch tests in 10 control subjects were all negative.

After obtaining the patient's informed consent, we performed a single blind oral challenge with allopurinol and tetrazepam. The results were negative for both drugs.

To investigate possible cross-reactivity between other non-steroidal anti-inflammatory drugs, we carried out a single blind oral challenge with acetylsalicylic acid, and the result was negative. We therefore recommended the patient to avoid propionic acid group drugs and take only the remaining non-steroidal anti-inflammatory drugs.

Fixed drug eruption is a non-immediate reaction that is well described in the literature.<sup>3</sup> The exact pathogenesis of fixed drug eruption is unknown.<sup>2</sup>

Patch testing is a simple and safe method to identify certain causative agents of fixed drug eruption, especially if residual lesions persist.<sup>2</sup> In our case, patch test with



**Figure 1** Patch test positive with ibuprofen 1% and 5% on the residual lesion.