

**Reverse Takotsubo Cardiomyopathy (rTTC) after a Severe Almond-dependent,
Exercise-induced Anaphylaxis**

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Nut allergy is one of the most frequent causes of anaphylaxis, often eliciting life-threatening reactions.

We are reporting a case of reverse Takotsubo cardiomyopathy (rTTC) in a patient after a severe almond-dependent, exercise-induced anaphylaxis in which a 7S globulin (vicilin) was identified as sensitizing allergen. rTTC is a rare variant of classic Takotsubo cardiomyopathy (TTC) that presents within a different clinical profile and specific hemodynamic support.

A 28-year-old woman with no previous personal history of atopy, suffered an episode of generalized urticaria, edema of the lips and hands, shortness of breath and consciousness loss after 30 minutes of running presenting to the emergency department with cardiogenic shock. Troponin I level was mildly elevated up to 2,7 ng/mL (normal <0,4ng/ml) with anterior ST-segment (V1-V4) elevation on ECG and left ventricular dysfunction on the transthoracic echocardiography (ejection fraction of 10-15%), with basal and middle segments hypokinesis. She received intramuscular adrenalin and intravenous antihistamine, noradrenalin and dobutamine treatment with symptom recovery. During her hospital admission, she underwent a normal coronary computerized axial tomography scan, a magnetic resonance imaging without myocardial oedema or scarring and her left ventricular ejection fraction was gradually recovered up to 60% so she fulfilled the diagnosis criteria for rTTC [1] after evaluation by the Cardiology Department and was sent to the Allergy Department for evaluation. Written consent for publication was obtained from the patient.

After a thorough anamnesis looking for possible etiological agents (allergens), the reaction happened early in the morning and, prior to going running she had only eaten almonds without any other food or drugs. Skin prick tests (SPT) were

performed by prick-by-prick test with nuts (almond, hazelnut, peanut, chestnut, sunflower seed, pine nut, walnut, pistachio, and cashew). SPT were also carried out with *Betula verrucosa* pollen (ALK, Spain) and purified protein: Pru p 3 (nsLTP) (Roxal, Spain). SPT was positive to almond (4mm) and hazelnut (10mm) and negative for the rest.

Baseline tryptase value was normal 3.48 $\mu\text{g/L}$. Specific IgE (ImmunoCAP, Thermo Fisher Scientific) was positive to almond 0.70 kU/L and hazelnut 1.23 kU/L. It was negative to peanut, chestnut, walnut, pistachio, cashew, sunflower seed and pine nut as well as to purified allergens: LTP (Ara h 9, Cor a 8 and rPru p 3), PR-10 (rAra h 8), profilin (Pru p 4), gluten, rAra h 1 (7S globulin), rAra h 2 (2S albumin) and rAra h 3 (11S globulin).

For *in vitro* experiments, walnut, almond and hazelnut extracts were provided by Roxal, Spain. The protein concentration was adjusted to 1 mg/mL. Immunoblotting assays was performed as previously reported [2] and revealed a 49kDa IgE-binding band in almond extract and three bands in hazelnut (60kDa, 49kDa and 14kDa) (Figure 1A). Immunoblotting-inhibition (preincubated with almond or hazelnut extract) revealed that the 49-kDa band in hazelnut was inhibited by the almond extract (Figure 1B). A 49-kDa band from almond extract and a 14-kDa band from the hazelnut extract were extracted from the gel and identified by mass spectrometry, as previously reported [2]. Research conducted with protein databases identified the 49 kDa protein as a vicilin and the 14 kDa band as a 2S albumin. Vicilins (7S globulin) are seed storage proteins from plants (seeds, nuts and legumes). Although several 7S globulins have been reported as nut allergens, we should emphasize that it is the first time that a 7S globulin from almond has been identified as an allergen.

The patient avoided almond after suffering the allergic reaction, although she continued eating other nuts without experiencing any adverse reaction. She tolerated exercise (running) well. A challenge with almond was not performed due to the severity of the reaction and the sensitization to almond. Although hazelnut was tolerated, we recommended that the patient avoid both almond and hazelnut

in the future, especially prior to exercising. Autoinjectable adrenaline and rescue medication were also prescribed.

Based on these data, the diagnosis was rTTC after a severe almond-dependent, exercise-induced anaphylaxis, in which the etiological agent was a 7S globulin (vicilin).

TTC also known as “stress cardiomyopathy” or “broken heart syndrome” is an acute but often reversible left ventricular dysfunction [3], usually triggered by emotional or physical stress. Several variants of TTC have been described based on the regions of the ventricular wall motion abnormality including the midventricular and basal wall. rTTC is a rare variant which presents with basal ballooning instead of apical ballooning. The Takosubo Registry showed that only 2.2% of TTC cases were rTTC [4].

Nut allergy is one of the most frequent causes of anaphylaxis [5]. The nuts eliciting allergy depend on the consumption habits, region of the world, environmental allergens as well as patient age [6,7] and the severity of the reaction has been linked to the purified allergen involved in the reaction [8]. Walnuts and hazelnuts were the most frequent nuts eliciting allergy in Spain [7], in spite that almonds were the second most consumed nuts [9].

Food-dependent, exercise-induced anaphylaxis is a severe allergic reaction in which symptoms develop if exercise takes place within a few hours of eating a sensitizing food. The patient had eaten almonds 30 minutes before developing an anaphylactic reaction and almond sensitization was shown both by positive skin prick-prick test and specific IgE. Immunoblotting revealed a 49 kDa IgE-binding band, identified as an almond vicilin (7S globulin) which appear to be the only purified allergen involved as etiological agent. In this sense, we must highlight that seed storage proteins have been linked to the most severe allergic reactions [8].

Curiously, the patient was also sensitized to hazelnut, showing sensitization to 7S globulin and 2S albumin. 7S globulin from hazelnut was cross-reactive with its almond homologue, but this was not demonstrated for the 2S albumin. Despite

sensitization to both proteins in hazelnut, the patient ate hazelnut without experiencing any adverse reaction. The patient has been shown good tolerance of exercise (running).

In summary, it is the first time that a 7S globulin (vicilin) was identified as a new almond allergen. It elicited a life-threatening reaction, a severe exercise-induced anaphylaxis complicated with a reverse Takotsubo cardiomyopathy.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Figure 1.

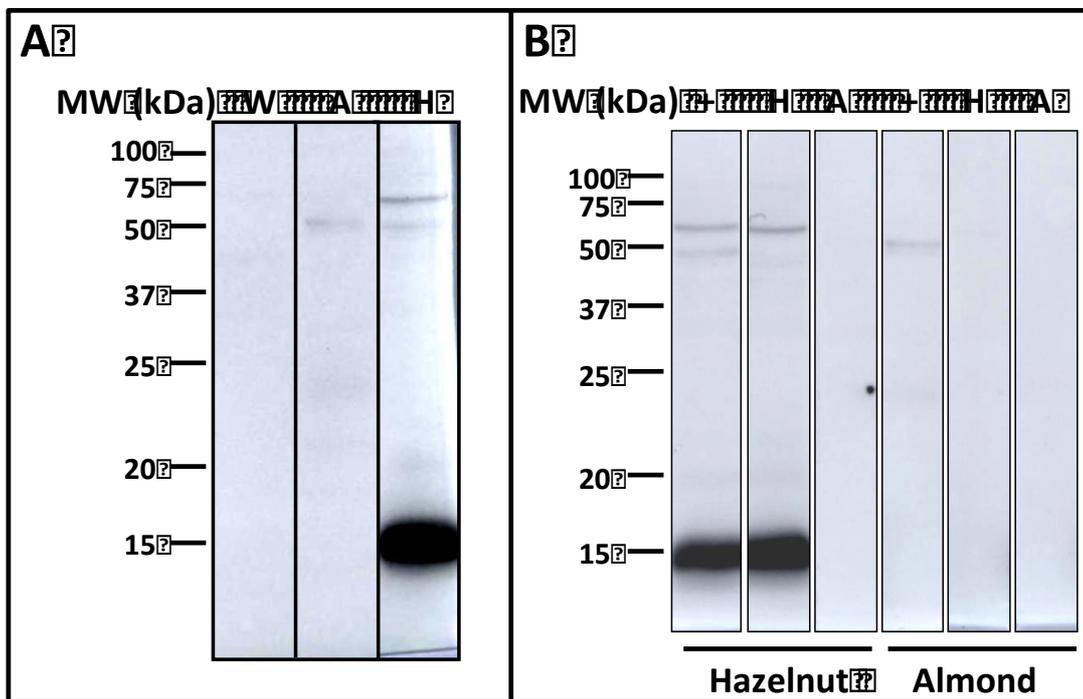


Figure 1 legend: **Panel A:** Detection of IgE-binding proteins in walnut [W], hazelnut [H] and almond [A] extract. **Panel B:** Immunoblotting inhibitions results. Lane +: patient's serum; Lane A: patient's serum inhibited with almond extract; Lane H: patient's serum inhibited with hazelnut extract. MW: Molecular weight marker.