Buckwheat-Induced Refractory Anaphylaxis in a Hospitalized Patient

Domínguez Estirado A[1], Cuevas Bravo C[1], Skrabski F[2], Baptista Serna L[3], Bartolomé Zavala B[4], Labrador-Horrillo M[5,6,7], Tornero Molina P[1]

[1]*Allergy Department, University Hospital Gregorio Marañón, Madrid, Spain*
[2]*Allergy Department, University Hospital Joan XXIII, Tarragona, Spain*
[3]*Allergy Department, QuirónSalud Hospital, Toledo/Talavera de la Reina, Spain*
[4]*R+D Department, Roxall, Bilbao, Spain*
[5]*Allergy Department, Vall d'Hebron Hospital, Barcelona, Spain*
[6]*Vall Hebron Institut Recerca (VHIR), Barcelona, Spain*
[7]*Universitat Autònoma Barcelona (UAB), Barcelona, Spain*

J Investig Allergol Clin Immunol 2024; Vol. 34(5): XX-XX
doi: 10.18176/jiaci.1001

Key words: Buckwheat. Refractory anaphylaxis. Celiac disease. 2S albumin.

Palabras clave: Trigo sarraceno. Anafilaxia refractaria. Celiaquía. Albúmina 2S.

Refractory anaphylaxis is an uncommon yet potentially fatal condition characterized by a lack of response to treatment with at least 2 doses of adrenaline 300 µg. It accounts for 0.37% of all cases of anaphylaxis. While drugs are the main culprits, it is imperative to recognize other triggers, including food sources [1].

We present the case of a 64-year-old man diagnosed with rhinoconjunctivitis due to sensitization to pollens, persistent asthma, nasal polyposis, and celiac disease who has been following a gluten-free diet for years. He was hospitalized in October 2021 with fever and kidney and heart failure. He experienced an episode of facial erythema, generalized urticaria, nausea, dyspnea, and dizziness. The physical examination revealed edema of the uvula. Cardiopulmonary auscultation was normal, blood pressure was 90/60 mmHg, and SpO_2 was 88%. Treatment included dexchlorpheniramine 5 mg, intravenous hydrocortisone 200 mg, intramuscular epinephrine 0.3 mg, and oxygen therapy, although symptoms persisted. Intramuscular epinephrine 0.3 mg was administered twice, to no avail. The patient required orotracheal intubation in the intensive care unit and administration of dexchlorpheniramine and hydrocortisone every 8 hours. Outcome was favorable within 24 hours.

One and 4 hours before onset of symptoms, the patient had received omeprazole and paracetamol, which he subsequently tolerated. He had not received other drugs in the previous 12 hours. Ten minutes earlier, he had eaten a croissant (buckwheat, psyllium [*Plantago*], dextrose, prolyl oligopeptidase, margarine, salt, egg, milk, yeast).

The medical interview revealed multiple episodes of upper respiratory tract symptoms due to inhalation of buckwheat flour while making bread, as well as generalized urticaria and dyspnea after ingestion of homemade bread. One of those episodes required administration of epinephrine in the emergency department. The patient tolerated other foods.

Skin prick test (SPTs) with raw buckwheat flour extract (dilution with saline solution 1:10) yielded a positive result (10×10 mm), as did prick-by-prick testing with the croissant (4×4 mm). Findings for 4 controls were negative. SPTs with commercial extracts of pollens from olive, grasses, *Salsola*, and *Plantago* were positive. Determination of specific-IgE (ImmunoCAP, Thermo Fisher Scientific) was negative (<0.10 kU_A/L) for peanut, rAra h 2, latex, coconut, soybean, wheat, rTri a 19, and *Plantago*. Total IgE was 29 kU/L. The serum baseline tryptase level was 4.47 µg/L.

The protein extract from buckwheat was prepared by homogenization in phosphate-buffered saline (20% wt/vol),

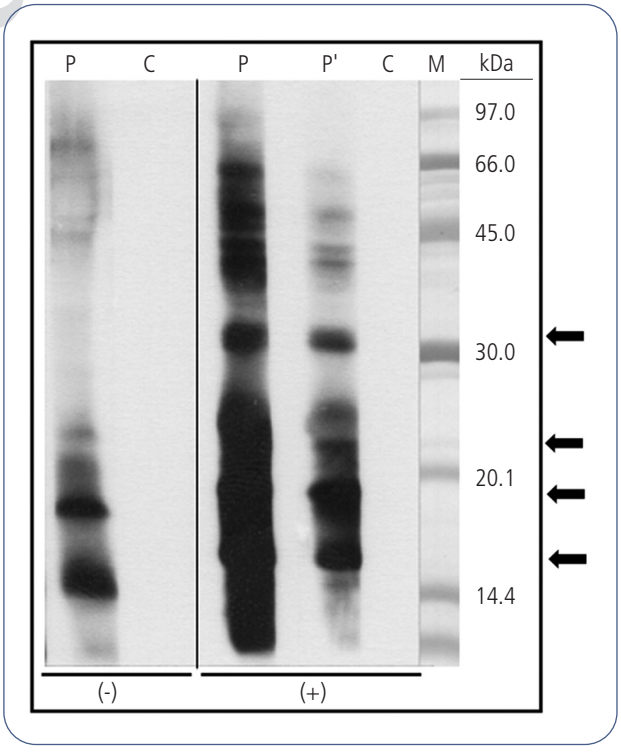

Figure. SDS-PAGE immunoblotting with buckwheat extract. Lanes P and P´, Patient serum, 2 dilutions; Lane C, control serum (pool of sera from nonatopic individuals); Lane M, molecular mass marker. (–) indicates without 2-mercaptoethanol; (+), with 2-mercaptoethanol.

dialyzation, and lyophilization. SDS-PAGE and immunoblotting were carried out under reducing conditions (2-mercaptoethanol) with buckwheat extract according to Laemmli [2]. The assay revealed 4 IgE-reactive bands of approximately 16, 19, 24, and 31 kDa (black arrows in Figure).

An in vitro molecular study was performed to measure sIgE against buckwheat (f11) using ImmunoCAP and 112 allergen components, including Fag e 2 (ImmunoCAP ISAC 112i, Thermo Fisher Scientific). The study confirmed sensitization to buckwheat with a level of 1.57 kU_A/L and to Fag e 2 (albumin 2S) with a level of 0.2 ISU-E, possibly corresponding to the 16-kDa protein detected in immunoblotting. Testing for specific IgE to Ole e 1, Ole e 9, Phl p 1, Phl p 5, and Sal k 1 was also positive. All other allergens present in ImmunoCAP ISAC were negative, including *Plantago* and markers for cross-reactivity, such as profilins, PR-10s, nsLTPs, and storage proteins.

We present a case of severe refractory anaphylaxis after intake of buckwheat. Fever could be a potential risk factor for the severe reaction. Asthma was well controlled, and no other cofactors were implicated. [3].

Up to 3% of anaphylactic reactions stem from buckwheat in Japan, while in Europe the prevalence remains unknown, likely at a markedly lower rate than in Asian countries [4]. Buckwheat (*Fagopyrum esculentum*) is a herbaceous member of the Polygonaceae family and bears no taxonomic ties to wheat. Originating in Central Asia, it has become enormously popular in Europe in gluten-free diets as a nutritious option that provides essential nutrients, including fiber, protein, and various vitamins and minerals. It is also used in baking as a substitute for wheat flour in many recipes (eg, pancakes, noodles, bread) and as a viable alternative for individuals with celiac disease. Sensitization to buckwheat can occur by food intake, inhalation of flour, and skin contact with pillows stuffed with its seeds [5-7].

The major allergens described are storage proteins. Fag e 1 (11S globulin β-chain, 24 kDa) is considered the main allergen, Fag e 2 (2S albumin, 16 kDa) is highly resistant to digestion and capable of causing severe reactions, and Fag e 3 (7S globulin [vicilin], 19 kDa) is a more specific marker of allergy to buckwheat and a predictor of severe reactions. Fag e 4 (hevein, 12 kDa), Fag e 5 (vicilin, 55 kDa), and Fag e 6 (albumin 2S, 10 kDa) are minor allergens.

Sensitization to buckwheat extract (f11) and Fag e 2 was verified by ImmunoCAP. Based on the molecular masses obtained by SDS-PAGE and immunoblotting, the 19-kDa protein detected is likely to be Fag e 3 (vicilin-like) and the 24-kDa protein, Fag e 1. Buckwheat sIgE levels do not always correlate with the severity of the reaction [8] and can be positive in asymptomatic patients, as occurs with Fag e 1 [9], thus illustrating the importance of component-based diagnosis. Quantification of sIgE against Fag e 2 and Fag e 3 is a better discriminator than sIgE to buckwheat. The specificity of sIgE against Fag e 2 is high (96%), although sensitivity is low [10]. Positive sIgE to Fag e 3 has been detected exclusively in persons allergic to buckwheat and can even predict severe symptoms, since patients with anaphylaxis had significantly higher levels [7].

When anaphylaxis occurs in a hospitalized patient, it is usually attributed to a drug. However, other causes are possible, and appropriate data collection from the patient's allergy history is very important. The prevalence of buckwheat allergy is currently very low in Europe, although with the increase in consumption of this food by celiac patients and the rise of gluten-free diets, both the number of cases and their severity may increase in the coming years.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Francuzik W, Dölle-Bierke S, Knop M, Scherer Hofmeier K, Cichocka-Jarosz E, García BE. Refractory anaphylaxis: data from the European anaphylaxis registry. Front Immunol. 2019;10:2482.
2. Laemmli UK. Cleavage of structural proteins during the assembly of the head of bacteriophage T4. Nature. 1970;227:680-5.
3. Turner PJ, Arasi S, Ballmer-Weber B, Baseggio Conrado A, Deschildre A, Gerdts J, et al. Risk factors for severe reactions in food allergy: rapid evidence review with meta-analysis. Global Allergy, Asthma European Network (GA2LEN) Food Allergy Guideline Group. Allergy. 2022;77:2634-52.
4. Imamura T, Kanagawa YA. A survey of patients with self-reported severe food allergies in Japan. Pediatr Allergy Immunol. 2008;19:270-4.
5. Park JW, Kang DB, Kim CW. Identification and characterization of the major allergens of buckwheat. Allergy. 2000;55:1035-41.
6. Norbäck D, Wieslander G. A review on epidemiological and clinical studies on buckwheat allergy. Plants. 2021;10:3-607.
7. Yanagida N, Sato S, Maruyama N. Specific IgE for Fag e 3 predicts oral buckwheat food challenge test results and anaphylaxis: A pilot study. Int Arch Allergy Immunol. 2018;176:8-14.
8. Tohgi K, Kohno K, Takahashi H. Usability of Fag e 2 ImmunoCAP in the diagnosis of buckwheat allergy. Arch Dermatol Res. 2011;303:635-42.
9. Choi SY, Sohn JH, Lee YW. Characterization of buckwheat 19-kD allergen and its application for diagnosing clinical reactivity. Int Arch Allergy Immunol. 2007;144:267-74.
10. Geiselhart S, Nagl C, Dubiela P, Pedersen AC, Bublin M, Radauer C, et al. Concomitant sensitization to legumin, Fag e 2 and Fag e 5 predicts buckwheat allergy. Clin Exp Allergy. 2018;48:217-24.

Manuscript received November 22, 2023; accepted for publication February 16, 2024.

Alicia Domínguez Estirado
Allergy Department
University Hospital Gregorio Marañón
Dr. Esquerdo, 46
28007 Madrid, Spain
E-mail: adominguezestirado@gmail.com