## Immunoglobulin G as a Milk Allergen

Saura Foix MP[1], Bartolomé B[2], Barrena Crespo J[3], Delavalle B[1], Izquierdo Domínguez A[1], Hernández Arauzo N[1], Castillo Marchuet MJ[1], Viñas Domingo M[1]

[1]*Allergy Service, Consorci Sanitari de Terrassa, Barcelona, Spain*
[2]*Roxall España, Department of I+D, Bilbao, Spain*
[3]*Pediatric Service, Consorci Sanitari de Terrassa, Barcelona, Spain*

J Investig Allergol Clin Immunol 2022; Vol. 32(4): 304-305
doi: 10.18176/jiaci.0746

Key words: Milk allergy. Anaphylaxis. Food allergy. IgG. Casein.

Palabras clave: Alergia a la leche. Anafilaxia. Alergia alimentaria. IgG. Caseína.

Allergy to cow's milk proteins is one of the most frequent allergies in childhood, and caseins are the main allergens involved [1]. Allergy to goat and sheep's milk casein without cross-reactivity to cow's milk casein was first described in 1995. Since then, several cases of food allergy to goat and sheep's milk have been described in patients who tolerate cow's milk [2]. A case of allergy to goat and sheep's milk caused by $\alpha$-2 casein was recently reported in a patient who tolerated cow's milk [3].

We present the case of a 12-year-old boy who was being followed in our department after experiencing 5 episodes of anaphylaxis. The patient had mild-intermittent allergic rhinitis and persistent moderate extrinsic bronchial asthma due to allergy to mites and cat epithelia. In August 2017, after ingesting chicken in batter and chocolate ice cream, he developed sneezing, rhinorrhea, and dyspnea. In September 2017, he experienced 2 reactions: one after eating salad with lettuce, tomato, carrot, mozzarella, cucumber, and tuna, in which he developed rhinorrhea and generalized urticaria; and another that was unrelated to food intake, in which he developed urticaria, rhinitis, and dyspnea. In January 2018, after eating spaghetti with carbonara sauce and a chocolate yogurt, he developed dyspnea and hives. His most recent episode occurred in February 2019 after eating a beef steak and loin stuffed with battered cheese and manifested as abdominal pain, hives, and dyspnea. The episode was not associated with exercise or drugs. The patient follows a free diet between episodes and tolerates cow's milk.

The allergology work-up consisted of skin tests with the foods involved and was positive for cow casein and goat and sheep's milk. Negative results were found for cow's milk, cow $\alpha$-lactalbumin, cow ß-lactoglobulin, egg, tomato, lettuce, carrot, peach, beef, chicken, tuna, shrimp, latex, *Anisakis*, profilin/Pho d 2, and peach nsLTP/Pru p 3. Negative results were also reported in prick-by-prick tests with raw and cooked turkey meat, raw and cooked beef, and tartrazine. Testing of unlabeled loin stuffed with industrial battered cheese was negative for samples from the outside and positive for samples

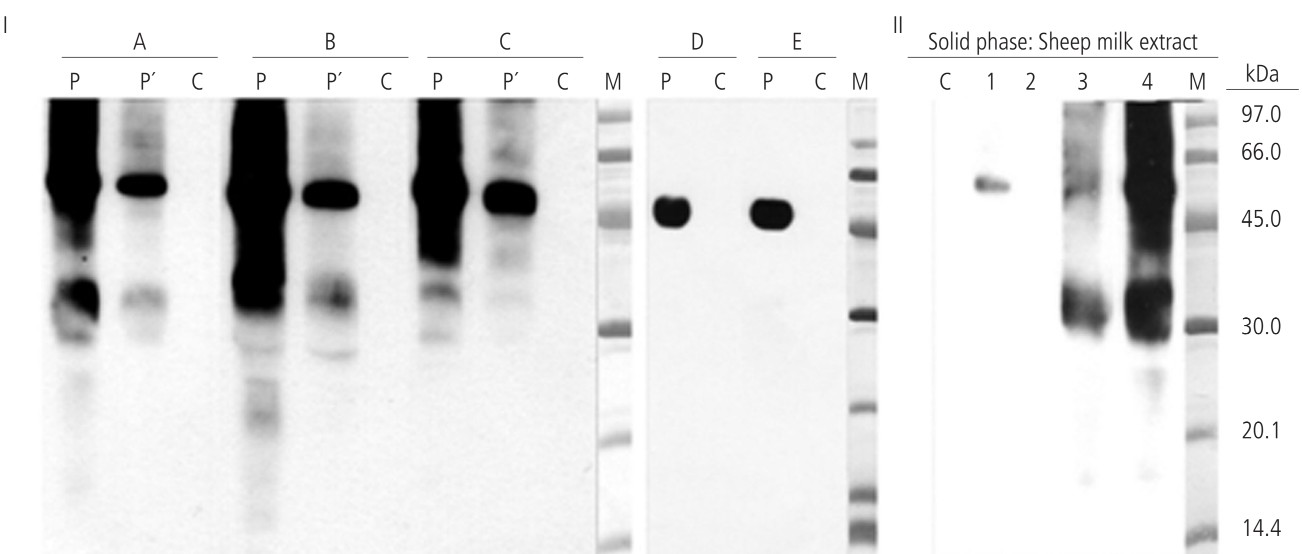


**Figure.** I, SDS-PAGE immunoblotting. A, indicates sheep's milk extract; B, goat's milk extract; C, cow's milk extract; D, goat IgG; E, sheep IgG. Lanes P and P′, patient serum (2 dilutions). Lane C, control serum (pool of sera from nonatopic persons). Lane M, molecular mass standard. II, SDS-PAGE immunoblotting-inhibition. Solid phase. Sheep's milk extract. Lane C, control serum (pool of sera from nonatopic persons); Lanes 1-4, patient serum preincubated with sheep's milk extract (lane 1), with goat's milk extract (lane 2), with cow's milk extract (lane 3), and with sunflower pollen extract (lane 4).

from the inside. The results of the complete blood count, biochemistry, and tryptase were normal. Total immunoglobulin E (IgE) serum was 229.9 IU/mL by ImmunoCAP (Thermo Fisher). Serum specific IgE levels by ImmunoCAP (Thermo Fisher, $kU_A/L$) were as follows: sheep's milk, 5.47; goat's milk, 9.52; cow's milk, 0.25; cow α-lactalbumin, <0.10; cow ß-lactoglobulin, <0.10; cow casein, 0.17; cow serum albumin (nBos d 6), <0.10; tartrazine, <0.35; α1.3 gal, <0.1; r Tri a 19, <0.1; and rPru p 3, <0.1.

Protein extracts from cow, goat, and sheep's milk were prepared by homogenization in phosphate-buffered saline (15% wt/vol) (50 mM phosphate buffer, 100 mM NaCl, pH 7.5), dialyzation against distilled water, and lyophilization. In order to study the molecular mass of the possible allergens, the 3 types of milk extract were studied with sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) immunoblotting as described by Laemmli [4] (with 2-mercaptoethanol). In all 3 extracts, the assay revealed an intense IgE-binding band of approximately 50 kDa and a much lighter zone around 33-30 kDa. As the molecular mass of the 50-kDa band matched with the heavy chain of the IgG, SDS-PAGE immunoblotting was carried out with purified goat and sheep IgGs and the patient's serum, and a band of 50 kDa was detected in both extracts (Figure, I). The presence of cross-reactive serum IgE was analyzed using SDS-PAGE immunoblotting-inhibition with the sheep's milk extract in the solid phase and the goat and cow's milk extracts as inhibitors. Total inhibition of IgE binding was observed in the goat's milk extract; partial inhibition was produced by the cow's milk extract (Figure, II).

Together with the higher serum IgE value detected against goat's milk extract than with sheep's milk and the absence of total inhibition of IgE binding observed with sheep's milk extract (homologous inhibition) as the inhibitor, these results lead us to suspect that goat's milk could be the primary sensitizer in the patient's milk allergy.

We therefore assume that the patient was first sensitized to goat's milk and presented allergic symptoms due to consumption of this milk and that, subsequently, owing to cross-reactivity, he reacted to sheep's milk proteins and developed allergic symptoms. The specific IgE recognizing IgGs and caseins from goat, sheep, and cow's milk detected in the patient's serum can justify an allergic reaction due to exposure, contact, or ingestion of these foods. However, in this case, sensitization to cow IgG must be produced by a cross-reactivity event that does not give rise to allergic symptoms. The band detected around 33 kDa in cow's milk was very faint, corresponding to the low specific IgE level detected in the ImmunoCAP assay against cow casein (0.17 $kU_A/L$). The patient was diagnosed with anaphylaxis resulting from food allergy to goat and sheep's milk, with appropriate tolerance to cow's milk. While allergy to sheep and goat's milk is rare, its frequency is increasing, and it must be taken into account in the context of idiopathic anaphylaxis. In the cases published to date in cow and sheep's milk allergy, the proteins involved are caseins [5,6]. Our literature review did not yield IgE-mediated sensitization to the IgG of goat and sheep's milk. Further clinical studies should be considered to confirm the importance and evolution of this sensitization.

*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.

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*Manuscript received May 28, 2021; accepted for publication August 10, 2021.*

**Mª del Pilar Saura Foix**
C/ Torrebonica, s/n
08227 Terrassa (Barcelona)
E-mail: saura.pilar@gmail.com