

Case report

Anaphylaxis from cow's milk casein

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The case of a 35-year-old woman who suffered anaphylaxis after the ingestion of milk or milk-containing products is presented. Symptoms also appeared after the patient used a cosmetic which contained casein. Skin prick tests, specific IgE measurement, and immunoblotting were carried out with cow's milk extract, and its purified proteins: casein, β -lactoglobulin, and α -lactalbumin. Specific IgE to cow's milk casein was detected with the three tests. Immunoblotting revealed one band of 24 kDa approximately corresponding to the β -fraction of casein. Negative results to β -lactoglobulin and α -lactalbumin were obtained with the three methods. Symptoms were controlled by rigorous dietary and behavior measures.

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Anaphylaxis due to cow's milk proteins is common in infants but rarely has its onset in adult life. Whey fractions (α -lactalbumin, β -lactoglobulin, and bovine globulins) are the most important allergens in milk (1), although associated sensitization to casein has also been reported (2). Few milk-allergy cases with onset in adult life have been published (3–7). In these cases, specific IgE was produced against more than one milk protein (3, 5, 7), and bronchospasm was the main symptom presented (4–6).

We report the case of a nonatopic woman, monosensitized to β -casein, in whom anaphylaxis followed ingestion of milk or milk-containing products, or the local application of cosmetics containing casein. Monosensitization to β -casein was proved by skin tests, specific IgE measurements, and immunoblotting.

Case report

A 35-year-old woman with no personal or family history of atopy presented with repeated anaphylaxis. During the 6 years before the onset of the symptoms, she reported gastrointestinal upset symptoms after ingestion of milk or milk-containing products. For the last 4 years, she had had attacks of neck pruritus which became generalized, with hives and tongue edema, nausea, vomiting, diarrhea, dizziness, tachycardia, profuse sweating, and death feeling. Every attack happened a few minutes after the ingestion of milk or milk-containing products

(cheese, butter, yogurt, etc). Emergency treatment was required several times.

She was put on a strictly milk-free diet, and self-injectable subcutaneous epinephrine was given to her. Nevertheless, she had three other attacks of palmoplantar itch and generalized urticaria when eating products with hidden milk. The first attack occurred after she ate an omelet to which milk had been added in a restaurant. She had eaten some purchased cakes (shortbread) before the second attack and "diet" mayonnaise before the third one; no milk or milk proteins were reported in either of these products.

She also had another attack of generalized skin pruritus, dizziness, tachycardia, and profuse sweating immediately after the application to her face of a make-up remover. She had never used it before, and the product proved to contain casein.

At present, the patient is asymptomatic, but she avoids eating or topically using any product of unknown composition and those which she has never eaten or used.

Material and Methods and Results

Cutaneous tests were performed with the skin prick test (SPT) as described (8). Besides a battery of the most common inhalant allergen sources in our area (mites, molds, pollens, and animal dander), we included cereals, egg, peanut, celery, mustard, and codfish.

Whole milk from three different species (cow,

goat, and sheep) and milk proteins (casein, α -lactalbumin, and β -lactoglobulin) were also tested. Extracts were provided by a pharmaceutical laboratory (Abelló SA, Madrid, Spain).

Positive results were obtained with cow's milk (7×7 mm) and with casein (5×5 mm). All the other extracts tested, including α -lactalbumin and β -lactoglobulin, were negative.

Specific and total IgE was measured with the Pharmacia CAP system. Total IgE was 7.4 kU/l, and specific IgE to cow's milk and casein were 8.90 and 3.70 kU/l, respectively. Specific IgE to the other milk proteins was negative.

SDS-PAGE (Fig. 1) was carried out according to Fling & Gregerson (9) at an acrylamide gradient concentration of 8–25%. Three types of commercial whole cow's milk (90 μ g of protein), purified bovine α -lactalbumin (30 μ g of protein), β -lactoglobulin (27 μ g of protein), and casein (25 μ g of protein) were used. The following polypeptides were used as MW markers: phosphorylase *b* (92.5 kDa), bovine

serum albumin (BSA) (66.2 kDa), ovalbumin (45 kDa), carbonic anhydrase (31 kDa), soybean trypsin inhibitor (21.5 kDa), and lysozyme (14.4 kDa). Electrophoresis was carried out in a vertical slab gel electrophoresis unit (Hoefer Scientific Instruments, San Francisco, CA, USA), and the protein bands were visualized with Coomassie brilliant blue.

Electrotransfer of proteins to nitrocellulose sheets was carried out according to Towbin et al. (10). The sheets were then incubated with the serum of the patient, washed, and finally incubated with Hamlet ^{125} I, a mouse antihuman IgE monoclonal antibody (Abelló SA, Madrid, Spain). IgE-binding proteins were visualized by autoradiography with appropriate exposure times.

Immunoblotting revealed one band of 24 kDa, corresponding to β -casein in whole cow's milk, which could not be demonstrated in raw casein (Fig. 2). Neither SDS-PAGE nor immunoblot detected any band in raw casein. IgE-binding

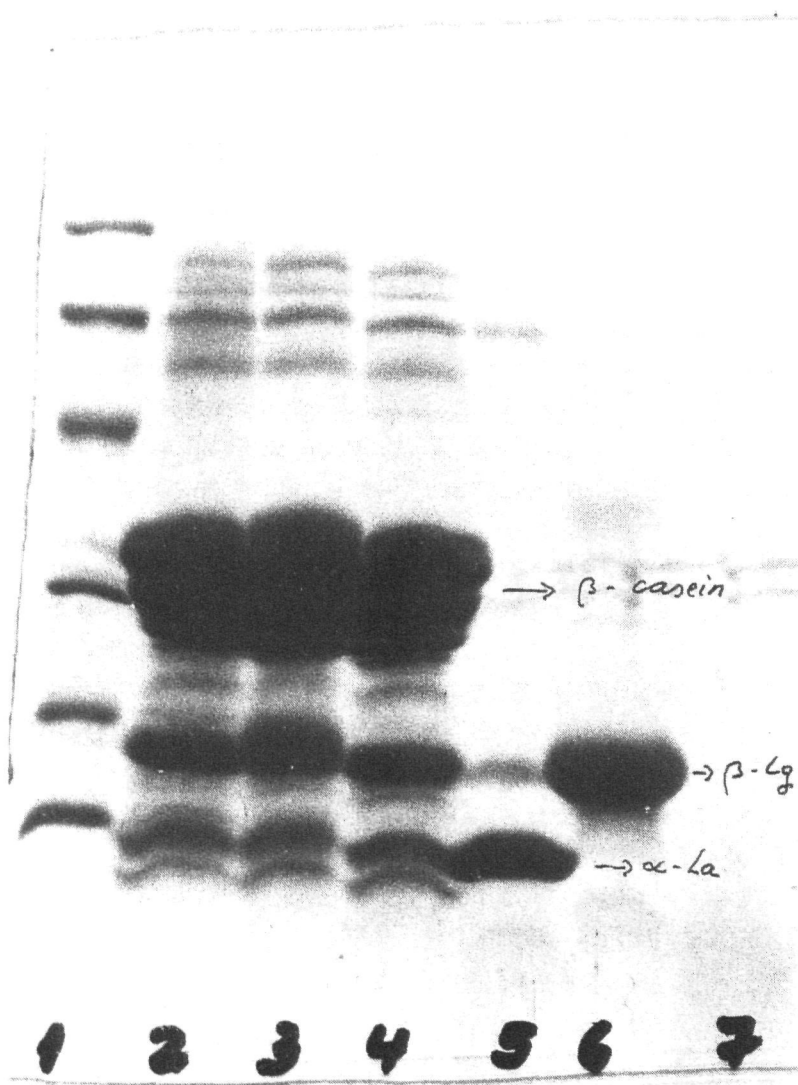


Fig. 1. SDS-PAGE according to Fling & Gregerson (9). MW markers (lane 1). We used three kinds of cow's milk, 2) whole milk, 3) powdered milk, and 4) pasteurized whole milk), and purified milk fractions: 5) α -lactalbumin, 6) β -lactoglobulin, and 7) raw casein). β -Casein (23.98 kDa), β -lactoglobulin (β -Lg) (18.26 kDa), and α -lactalbumin (α -La) (14.17 kDa) were visualized.

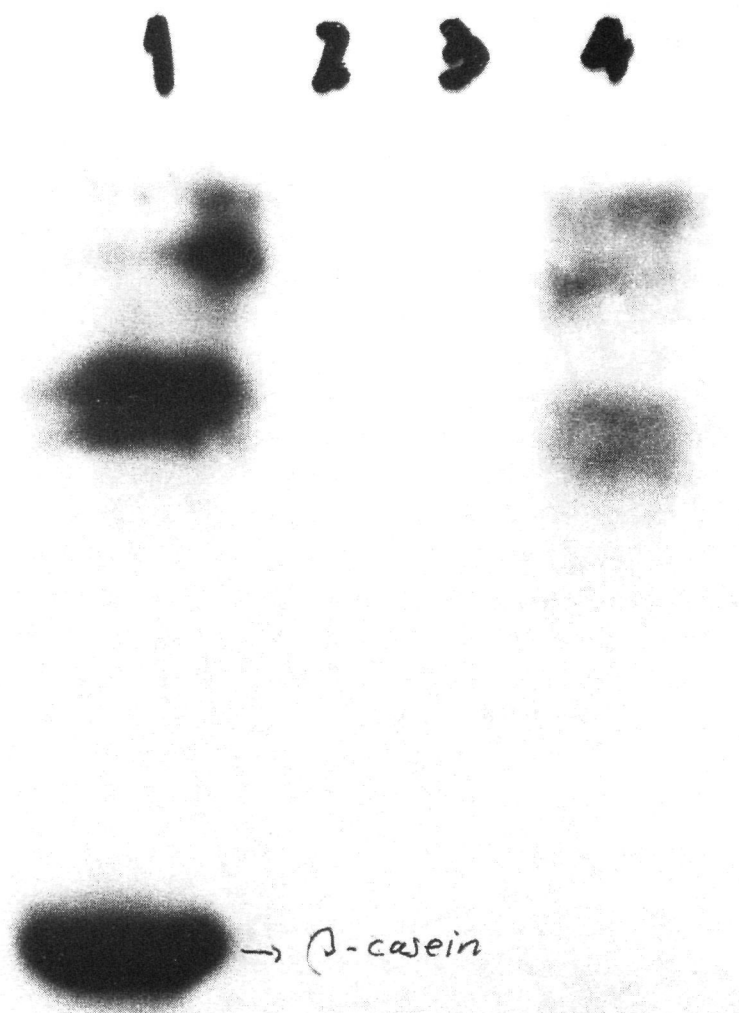


Fig. 2. Immunoblot of extracts performed with serum of patient. Lane 1) powdered milk, 2) α -lactalbumin, 3) β -lactoglobulin, and 4) raw casein. One band of 24 kDa, corresponding to β -casein, was revealed in whole cow's milk. No IgE binding to α -lactalbumin or β -lactoglobulin was revealed.

proteins in the range 66.2–92.5 kDa were also revealed in both casein and whole milk. This binding was regarded as unspecific. No IgE-binding to α -lactalbumin or β -lactoglobulin was revealed.

Discussion

Cow's milk proteins are subdivided into two fractions: casein and the whey fraction (composed of α -lactalbumin, β -lactoglobulin, bovine immunoglobulin, and albumin). Eighty percent of cow's milk protein content is casein. This heat-stable protein fraction is composed of five basic proteins: α -, α_s -, β -, κ -, and γ -casein. Cow's milk allergy has been considered one of the most common causes of food allergy among infants (1). Although Goldman et al. (11), in 1963, reported casein to be the milk protein most often giving positive SPTs among children with positive oral challenge with milk, their results have subsequently been attributed to contamination of the casein fraction with whey proteins (1). IgE-mediated cow's milk allergy has been mainly attributed to whey-protein fractions, and casein hydrolyzed formulas have been indicated for years among children who do not tolerate milk proteins (12). Nevertheless, anaphylaxis after ingestion of this formula (2) or contact with drugs containing casein (13) has been reported among milk-sensitive children. Casein IgE-mediated allergy has also been described as a source of occupational asthma in several jobs: tannery work (14), delicatessen work (7), and cattle farming (15).

A few cases have been reported of allergy to cow's milk among adults (3–7). Sensitization to both α -lactalbumin and casein was observed in the three reports in which IgE determination of milk fractions was carried out (3, 5, 7). The ingestion of milk or milk-containing products caused mainly respiratory symptoms (4–7) in the subjects, and anaphylaxis was reported in only one of them (3).

A 24-kDa band corresponding to β -casein was revealed in the immunoblot when whole milk was used as solid phase, but not when purified casein was used. Casein precipitates easily, and the fact that neither SDS-PAGE nor immunoblot revealed any band in raw casein might be due to its denaturation. The IgE-binding proteins of 66.2–92.5 kDa in raw casein and whole milk might be due to aggregates of precipitated casein or, what is most probable, to nonspecific IgE binding. The molecular weights of both α -lactalbumin and β -lactoglobulin are below the 24 kDa of casein, and no IgE captation could be detected in this area in whole milk or purified proteins. To our knowledge, no other case of adult onset food anaphylaxis due exclusively to casein has been reported in the literature. Our patient was monosensitized to the β -casein cow's milk fraction,

being skin-test negative, as well as specific IgE and immunoblotting negative, to whey proteins.

Casein is used in making other foods such as pork-derived products (cured ham, sausage, salami, etc.), unfermented grape juice, tiger nut milk, other fruit juices, and alcoholic drinks (wine, spirits, beer, natural alcohol-derived drinks, champagne, etc.). Thus, the exclusion diet for patients who have severe attacks after eating products containing casein should include many foods other than milk and milk-containing products.

As previously described in an infant (13), our patient was able to detect small amounts of casein contained in topical application products. Therefore, patients should also be advised to scrutinize the ingredients of any new drugs or cosmetics that they have not used before.

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