

COW'S MILK HYPERSENSITIVITY IN AN ELDERLY WOMAN: CLINICAL AND IMMUNOLOGIC FINDINGS

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We report a case of allergy to cow's milk diagnosed in a 79-year-old woman, who had the habit of drinking large amounts of milk and other dairy products for several years. She had been an asthmatic since the age of 40. At age 65, she noticed a correlation between cheese and milk intake and onset of asthma and two episodes of shock, and she has been avoiding milk for the past 15 years. Positive skin prick tests for cow's milk proteins, grass pollens, and house dust mite were observed. Serum IgE levels were above 3,000 U/mL, with high molecular weight IgE detected by gel chromatography. RAST results confirmed the presence of sensitizations detected by skin prick tests. The patient never suffered from atopic eczema. This unusual case of food allergy with onset after the age of 40 may indicate that prolonged exposure to food antigens in predisposed individuals may lead to the development of allergy even in adult age, lasting for decades after partial elimination of the allergen from the diet.

Abbreviations

ALA. α -lactalbumin
BLG. β -lactoglobulin
IC. immune complex
KgBA. conglutinin binding assay
LFT. liver function tests
SP. solid phase radioimmunoassay

Introduction

FOOD ALLERGY is quite easily diagnosed in infants and children by clinical history, skin tests, RAST, elimination diet and, when indicated, properly conducted food challenges. Symptoms generally include atopic eczema, gastrointestinal disorders, urticaria, asthma, or a combination thereof.^{1,2} It is commonly accepted that the incidence of food allergy tends to decline with age, as well as antibodies to food antigens,³⁻⁵ and a decrease of IgE production.^{5,6} Recently, Bock³ reported that well documented food allergy is still present in over 50% of young patients after a follow-up of 4 years. Cow's milk

was most common in those patients, who no longer presented a positive double-blind food challenge. His paper and others^{1,7} agree on the fact that cow's milk is the most frequent allergen in infants and children, but rarely, if ever, implicated in adult food allergy. Furthermore, in adult cases of food allergy, the diagnosis relies mainly on food elimination and oral challenges, since skin tests and RAST are usually negative.^{1,3} Symptoms in adults are often atypical, and mechanisms other than type I hypersensitivity have been postulated.

We report a case of food allergy with typical symptoms and onset in adult life, presenting *in vivo*, and laboratory evidence of type I hypersensitivity to cow's milk as well as to inhalant allergens, diagnosed when the patient was at the age of 79.

Case Report

The patient, M.G., a female 79 years old, was born in a village near Benevento (southern Italy). She had no family history of atopy; one sister had late onset diabetes. Married at the age of 20, she had three sons and four daughters, all in apparent good health; none was reported to be atopic. A farmer herself, after marriage she undertook to sell the milk from her husband's farm, and continued in this occupation for several years. Since the age of 21, she had the habit of drinking most of the unsold milk at dinner and her calculated

average daily intake exceeded 1 to 2 L of fresh milk for the following 20 years. Asthmatic episodes were occasionally reported at the age of about 40, and then became more frequent. No correlation with season, daily occupation, particular efforts, or eating habits was noticed until 25 years later when she no longer had milk every day. At 65, the patient found that wheezing occurred more frequently after eating cheese, and two sudden collapses at a few days' interval, perhaps shocks, followed the intake of fresh cow's milk. This prompted the discontinuation of milk, but not other dairy products. Occasional asthmatic attacks occurred during the following years, and sneezing fits were also present. At age 73 the patient required haemorrhoidectomy, then she underwent surgical excision of cutaneous cysts at 76 and colecystectomy for bile stones at 77. One year later she moved to a new house, and since then she only had one asthmatic crisis. For this reason she came to our observation at the S. Cuore Hospital in Benevento. At that time, the patient was not suspected of having atopic disease, but medical and EKG examination ruled out cardiac asthma. Her hemoglobin was 12.5 g/dL; erythrocyte sedimentation rate, 42 mm/h; and white blood cell count 7200/mm³ with 3% eosinophils. There were normal values of blood glucose, blood urea nitrogen, LFT, bilirubin, creatinin, transaminase, alkaline phosphatase, electrolytes, and a normal serum electrophoretic pattern. Low serum iron (65 μ g/dL) was found. The chest x-ray film was normal, and urinalysis showed many casts with well preserved erythrocytes in the sediment.

When the suspicion of bronchial asthma was raised, skin prick testing was also performed on several sessions during hospitalization, using Hollister extracts (Bayro-pharm, Italy) and repeated 6 months later as an outpatient with identical results. At this time no recent history of drinking cow's milk was obtained, but soft and hard cheese were a normal part of the patient's diet. Serum samples were collected before hospital discharge and stored at -20 °C in small aliquots until analysis.

Methods

Standard and Control Sera

The WHO standard 69/204 (reconstituted as directed, containing 10,948 IU/mL of IgE) as well as the Pharmacia (Uppsala, Sweden) standards for the PRIST-IgE kit were used both for determination of serum IgE levels and for chromatographic separations as controls. Twenty sera from normal donors and three sera from patients with rhinitis and asthma, with allergy to grass pollen or house dust mite, and high IgE values were used as controls respectively for determination of class specific antibodies to cow's milk proteins and gel chromatography studies.

Serum IgE Levels

The paper radioimmunosorbent test (PRIST-Pharmacia) was used with the standards described.

IgE Antibodies

These were detected by radioallergosorbent test (RAST-Pharmacia) using commercial kits for the following allergens: cow's milk, house dust (Hollister), *Parietaria officinalis* (pellitory), *Lolium perenne* (rye grass), covalently linked to paper discs. Results were expressed according to the Pharmacia RAST class score.

Other Antibody Classes

The SP-RIA described for detection of IgG to cow's milk BLG^{8,9} was adapted to measure specific IgA and IgM by substituting radiolabelled monospecific antisera to these Ig classes (Nordic). Determination of antibodies to ALA was made on ALA-coated plates using the same SP-RIA method. Both BLG and ALA were purchased through Sigma Chem Co, St Louis, MO, USA.

Detection of Circulating Immune Complexes

¹²⁵I Clq precipitation in 2.5% polyethylenglycol, as described by Zubler et al.¹⁰ and the KgBA, as described by Casali et al.¹¹ modified for specific detection of IgG and IgA complexes, were used to quantitate IC in fraction samples obtained by chromatographic separation.

Gel Chromatography

The WHO standard and the controls' and patient's sera were separated on a Sephacryl S-200 column, dimensions 28 $\times$ 2.6 cm, calibrated for 1-mL samples. Void volume detected by Blue dextran exclusion was 52 mL; each fraction was 2.3 mL. Samples were run at 2 mL/cm/h in Tris-HCl buffer 0.1 M, pH = 8, containing 0.5 M NaCl. Each chromatographic fraction was immediately tested for IgE content by PRIST, and for IC determination by Clq and KgBA techniques as described.

Results

Serum IgE levels were very high in this patient and duplicate samples repeatedly gave mean levels of 3200 U/mL. Dilutions from 1:10 to 1:10,000 were analysed with both types of standards.

RAST showed class 3 positive values for cow's milk, class 2 for *Lolium perenne* and *Parietaria* pollens, and class 1 for house dust (Hollister). RAST for other foods, eg, peanut and egg white, were negative. Because of the high IgE content, the serum was tested also at 1:10 to 1:100 dilution along with known positive and negative control sera. The serum remained positive for cow's milk although of lower intensity (Table 1).

The relationship of RAST results to skin prick tests is reported in Table 1. Concordance was observed for cow's milk, *Parietaria*, and grass pollens. *Dermatophagoides* spp. were used for skin testing, but house dust extract in the RAST. This might have lowered the intensity of the RAST value.

Class-specific antibodies to cow's milk BLG and ALA, assessed by SP-RIA, is reported in Table 2, comparing controls' and patient's results. The serum of

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Table 1. Relationship of *in Vivo* and *in Vitro* Tests for Detection of Specific Sensitizations*

Allergen	RAST Class	Skin Prick Test
House dust (H/S)	1	++
Dermatoph. pteron.	N.T.	++
Rye grass (Lolium)	2	++
Parietaria off.	2	++
Moulds (Alternaria)	0	Neg
Cow's milk	3	++++
Goat's milk	N.T.	Neg
Egg white	0	Neg

* Results of skin prick tests with Hollister-Stier extracts and RAST values (Pharmacia class scoring system) in patient M.G. House dust paper discs for RAST were coated with Hollister-Stier reagent; class 3 positivity to cow's milk was also tested at 1:10 and 1:100 dilutions of serum, and were class 2 and class 1, respectively. Wheal reactions were considered ++ when diameter reached 10 mm and ++++ in presence of pseudopods. N.T. = not tested.

M.G. contained high amounts of specific IgE, but little IgG, IgA, and IgM antibodies to the main whey proteins in cow's milk. This seems to be confirmed by the lack of precipitin lines in agar gel double immunodiffusion (results not shown).

The elution profile of serum M.G. on Sephacryl S-200 is shown in Figure 1. The fractions obtained by gel filtration were further analysed for IgE content by PRIST. Bound cpm are represented by the histogram in Figure 1; total IgE recovery was approximately 80%. The second elution profile represents monomer IgE contained in the WHO standard, shown for comparison. Three sera from atopic patients with high IgE levels were run under the same conditions as additional controls. In these latter cases IgE eluted in a sharp peak, positioned at 62- to 72-mL volume, similar to that found for monomer IgE (RP et al, manuscript in preparation).

The high molecular weight fractions (47- to 62-mL volume) were also tested for C1q binding and KgBA class specific immune complexes and resulted variably but definitely positive for IgG and C1q binding IC (Figure 1), suggesting the presence of aggregates containing macromolecular IgG.

Discussion

We described an unusual case of food allergy in an atopic woman aged 79, who developed asthma for the first time at about the age of 40. Multiple sensitizations to grass and Parietaria pollens, and house dust mite were also observed, but cow's milk was perhaps the most relevant allergen. Intense wheal-and-flare reac-

tions were induced by skin prick testing, which is an unusual finding at her age.^{3,12} Several authors have concluded that skin tests are not a useful tool in elderly patients.^{1,12} This is due to both immunoregulatory changes leading to decreased IgE production^{5,7} and diminished skin reactivity.^{5,6} The working and living environment provided a rich source for inhalant allergens, and the patient's habit of drinking large amounts of fresh cow's milk for decades was a possible cause for sensitization to this food. The finding of very high levels of serum IgE and the RAST results confirm that the patient is atopic and hypersensitive to these allergens.

Atopic patients seem to have an increased intestinal permeability to undigested macromolecules such as food proteins^{13,14} and this might help to explain the occurrence of sensitization in our case. It would be tempting to speculate that, provided adequate stimulation, atopic subjects might become sensitized to certain foods even in adult life.

We think that cow's milk proteins were the most important allergens because of the lack of seasonal variation of her symptoms and the fact that specific skin and RAST tests were more intensely positive for milk than for any other allergen. We cannot of course rule out the possibility that single episodes have been caused by other allergens or their combination. Unfortunately her age and condition made bronchial or oral provocation tests impractical and potentially very dangerous.

In this case, IgE was the only antibody class to cow's milk above normal control values (Table 2). This pattern of antibody response differs from that described in food allergic patients of younger age,^{4,8,15} who usually have increased amounts of specific IgG and other classes in addition to specific IgE. The decline of food allergen-specific IgE with age has been considered to be a constant event⁴ and cow's milk is not thought to play an important role in adult allergy.^{1,3} A "natural" hyposensitization to most allergens has been postulated to occur in elderly age⁶ but our patient demonstrates that the reverse may occur when constant stimulation is provided.

The finding of high molecular weight IgE and other Ig-containing macromolecular complexes in this patient's serum contrasts with previous results obtained by us in food-allergic patients^{2,9,13} showing circulating complexes containing IgE, IgG, and IgA only after oral

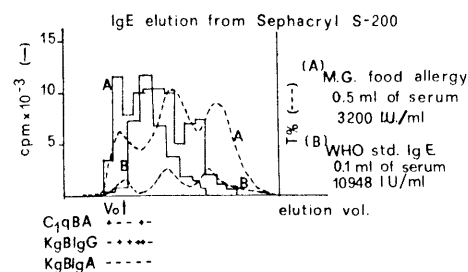


Figure 1. Histograms representing chromatographic elution of IgE in case M.G. and the WHO standard 69/204 (indicated as A and B samples). Results are shown as net counts/min, after background subtraction, for each fraction obtained.

challenge. We postulate that serum IgE, either monomer or in high molecular weight form, may play a role in the patient's recurrent respiratory symptoms.

This unique case suggests that despite the generally accepted decline of IgE production with aging,^{6,12} a profound imbalance in responses may be present in older age, possibly due to defective immunoregulation.^{16,17} This might also explain the persistent IgE response even after 15 years of cow's milk-free diet, although strict allergen avoidance has not been fully achieved. One practical and clinical implication of our report is that the possibility of late onset food allergy should not be overlooked in elderly cases presenting with unexplained asthma and high serum IgE levels.

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Table 2. Serum Antibodies to Cow's Milk and Isolated Proteins*

Serum	Antigen	IgG	IgA	IgM	IgE
M.G.	Cow's milk	723	N.T.	N.T.	3213
	BLG	245	180	384	N.T.
	ALA	239	N.T.	N.T.	N.T.
Controls (n = 20)	Cow's milk	1217 ± 313	N.T.	N.T.	258 ± 62
	BLG	326 ± 98	234 ± 90	549 ± 218	N.T.
	ALA	302 ± 97	N.T.	N.T.	N.T.

* Isotype specific antibodies to cow's milk and isolated proteins (BLG and ALA) by RAST and SPRIA tests. Results are reported as net counts/min bound. IgE RAST for cow's milk was inhibited by more than 50% with BLG and ALA (50 µg/mL) to confirm binding specificity. N.T. = not tested.

Use it up, wear it out;
Make it do, or do without.

New England Maxim