

Short communication

Milk hypersensitivity – key to poorly defined gastrointestinal symptoms in adults

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Lactose intolerance is a common adverse reaction to milk in adults, while milk hypersensitivity is a disorder of infancy. We hypothesized that milk hypersensitivity may cause many unspecific gastrointestinal disorders in adults. Twenty adults were subjected to double-blind, placebo-controlled milk challenge. Phagocyte activity, and Fc γ and complement receptor expression of phagocytes were assayed, and serum total IgE, milk-specific IgE, and serum reactivity to milk protein were determined. The challenge increased phagocyte activity and complement receptor expression of phagocytes in subjects designated milk-hypersensitive, who had gastrointestinal symptoms from milk ingestion but normal lactose tolerance. The increase was not detected in lactose-intolerant or control subjects. The milk-hypersensitive group was also distinguished from the lactose-intolerant group by enhanced serum reactivity to milk protein. Only two out of nine milk-hypersensitive subjects had detectable milk-specific serum IgE. It is concluded that milk hypersensitivity in adults, occurring as gastrointestinal reactions, may be more common than previously thought.

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Symptoms caused by milk are a vast problem, especially at an early age: about 20–40% of children are reported to have symptoms after consuming milk (1, 2), whereas, in adults, symptoms from milk vary widely between different populations (3). Adverse reactions to milk may be classified as lactase deficiency or as milk hypersensitivity which is mediated by immune mechanisms. Lactase deficiency occurs mainly in adults, while milk hypersensitivity is a problem mainly during infancy, particularly in atopic infants (4–6). Milk hypersensitivity exists in approximately 2.5% of the general infant population (1, 2, 7), as opposed to an incidence of 54% of the atopic population (6). Atopic diseases are in the process of augmentation; therefore, hypersensitivity disorders are expected to be more common and severe.

Lactose may not be the only component in milk causing frequent adverse reactions in adults (8). Most allergy textbooks suggest that milk hypersen-

sitivity is rare in adults, and only a few case reports (9–13) and studies (14–16) indicate milk protein as the antigen responsible for hypersensitivity reactions in adults. The symptoms arise from the skin, and the respiratory and gastrointestinal tracts; typically, several target organs are affected. This indicates a heterogeneity in symptoms of milk hypersensitivity in adults.

We hypothesized that milk hypersensitivity is more common among adults than previously reported. Therefore, we subjected milk-tolerant and -nontolerant adults to double-blind, placebo-controlled milk challenge; assayed phagocyte activity, and Fc γ and complement receptor expression of phagocytes (17); and determined serum total IgE, milk-specific IgE, and serum reactivity to milk protein.

Material and methods

Subjects

Inclusion criteria required that the randomly selected subjects ($n=20$, 15 women, five men, aged

Abbreviations. CR: receptor for complement fragment; Fc γ R: receptor for constant (Fc) region of IgG.

Table 1. Clinical characteristics of control subjects, subjects with lactose intolerance, and subjects with milk hypersensitivity

	Sex	Age (years)	Symptoms on milk-containing diet	Intensity of symptoms	Improvement of symptoms on milk elimination	Serum total IgE (kU/l)	Milk-specific IgE (kU/l)
Controls							
1	F	24	F, AB	+	—	19	<0.4
2	F	27	P, AB, F, B	+++	—	9	<0.4
3	F	23	F, P, AB	+	—	<5	<0.4
4	F	30	AB, F, B, D	++	—	36	<0.4
5	F	23	—	—	—	15	<0.4
6	M	26	F, D	+	—	17	<0.4
Lactose-intolerants							
7	F	55	—	—	—	17	<0.4
8	F	25	P, AB, F, B, D	+	—	73	<0.4
9	F	33	F, D, B	++	—	20	<0.4
10	F	27	F, B, D, AB	++	+	13	<0.4
11	M	35	AB, F, B, D	+++	+	50	<0.4
Milk-hypersensitives							
12	F	21	P, AB, F, B, D	++	+	275	<0.4
13	F	27	P, F, B, AB, D	++	+	10 100	3.3
14	F	24	P, AB, F, D	+++	+	15	0.7
15	F	25	P, AB, F, B, D	+++	—	26	<0.4
16	F	23	P, AB, F, B, D	+	+	42	<0.4
17	F	29	P, AB, F, B, D	++	+	<5	<0.4
18	M	36	AB, F, B, D	+++	+	<5	<0.4
19	M	26	F, D	++	+	112	<0.4
20	M	28	P, AB, F, B, D	+++	+	274	<0.4

Symptoms: P: abdominal pain; AB: abdominal bloating; F: flatulence; B: borborygmi; D: diarrhea. Intensity of symptoms: —: no symptoms; +: mild; ++: moderate; +++: severe.

21–55 years, mean 28 years) be free from signs and symptoms of acute infection and not have received any medication during the previous month. One of the subjects had mild hypertension and one was atopic, suffering from asthma and atopic dermatitis. By interview, seven of the study subjects were found to be milk-tolerant, whereas 13 were nontolerant and consistently and repeatedly reported gastrointestinal symptoms after milk consumption. Symptoms reported are presented in Table 1. A lactose tolerance test with ethanol was conducted to identify subjects with lactase deficiency (18). One of the tolerant subjects and four of the nontolerant subjects had lactase deficiency, and these were designated the lactose-intolerant group ($n=5$). Nine of the nontolerant subjects had normal lactose-tolerance-test results. The control group ($n=6$) consisted of milk-tolerant subjects with normal lactose tolerance. Informed consent was obtained from participants, and the study protocol was approved by the Committee on Ethical Practice of Tampere University Hospital.

Study design

In the double-blind, placebo-controlled, crossover milk challenge, the placebo was potato flour and the vehicle was fermented oatmeal cereal (Bioferme Ltd, Kaarina, Finland). Milk was low-fat and

low-lactose milk powder (Valio Ltd, Helsinki, Finland). In reconstituted form, the milk contained 34 g/l protein, 4 g/l β -lactoglobulin (19), and 0.5 g/l lactose. The amount of milk powder in the 3-day challenge period equaled 1 l of milk. Milk was consumed twice a day, equaling 400 ml per day. Subjects consumed milk at home, because, according to clinical history, no subject was expected to have reactions that might need clinical care. The sequence of the challenges was randomized. Each challenge period was preceded by 1-week milk-free diet, and after the first challenge period, there was a 1-week washout period on normal diet. During the study, subjects recorded their symptoms and the intensity of the symptoms.

Measurements

Peripheral blood samples were collected before and after the challenge periods. Leukocytes were isolated by lysing the erythrocytes with 0.83% ammonium chloride. Receptor expression and phagocyte activity were measured as previously described (17). In short, monoclonal antibodies and flow cytometry were used to assay the expression of the Fc_γ receptors (Fc_γRI, Fc_γRII, Fc_γRIII) and complement receptors (CR1, CR3) on granulocytes and monocytes. Phagocyte activity was measured with a luminometer using luminol-amplified

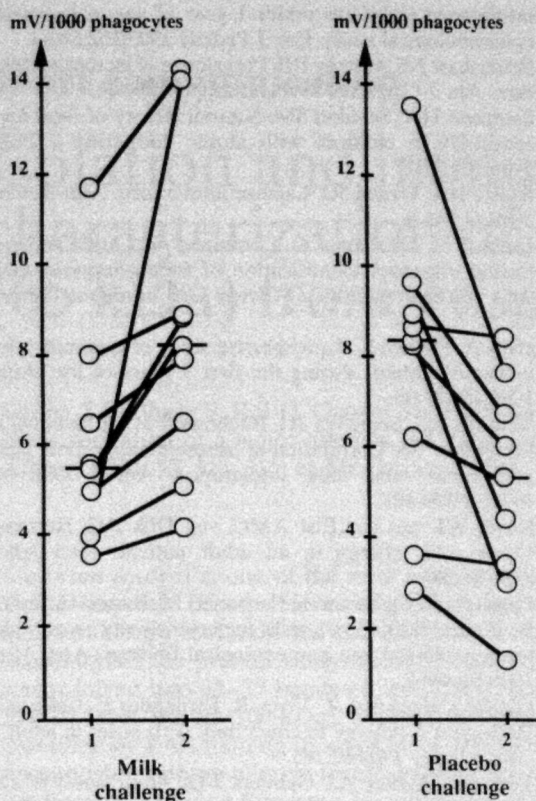


Fig. 1. Changes of phagocyte activity in isolated leukocytes with unopsonized zymosan produced before (1) and after (2) milk and placebo challenges in milk-hypersensitive subjects. Medians are presented as horizontal lines.

chemiluminescence as an indicator of the capacity of phagocytes (in diluted blood or isolated phagocytes) to produce reactive oxygen species after stimulation with unopsonized or opsonized zymosan. Data were recorded as millivolts (mV)/1000 phagocytes. Serum reactivity to milk protein was measured by incubating serum in milk protein-coated (66 µg milk protein from pasteurized, homogenized milk) polystyrene tubes. The capacity of antigen-antibody complexes to activate leukocytes was measured by removing serum and adding 100 000 isolated leukocytes, in Hanks' balanced salt solution supplemented with 0.1% gelatin and 0.4 mM luminol, to the tubes. The reaction was measured (mV) with a luminometer for 30 min at 37°C. The serum total IgE concentration (Ciba Corning Diagnostics, Halstead, UK) and milk-specific IgE (Pharmacia CAP System, Pharmacia AB, Uppsala, Sweden) were determined.

Statistics

Data are presented as median and interquartile range. The Mann-Whitney, Kruskal-Wallis, and Wilcoxon signed rank tests were used in statistical comparisons.

Results

As shown in Fig. 1, milk challenge increased ($P=0.007$) and placebo challenge decreased ($P=0.007$) the phagocyte activity of isolated leukocytes in the nine subjects clinically nontolerant of milk but with normal lactose tolerance. They were designated the milk-hypersensitive group. The same increase in phagocyte activity was observed after milk challenge in whole blood with opsonized zymosan ($P=0.05$). The challenge increased the frequency of complement receptors in granulocytes: median (lower quartile-upper quartile), CR1 before, 50 (45-63), and after the challenge, 70 (56-112) ($P=0.02$); and CR3 before, 500 (439-640), and after, 690 (498-1489) ($P=0.05$). The same result was observed for CR1 in monocytes ($P=0.02$). Milk challenge did not modify phagocyte activity or receptor expression in the control or in the lactose-intolerant group except for increased CR1 in granulocytes in the lactose-intolerant group ($P=0.04$). Serum reactivity to milk protein was higher in the milk-hypersensitive group, 147 (118-265), than in the lactose-intolerant group, 42 (32-79) ($P=0.001$).

As indicated in Table 1, the serum total IgE concentration was comparable in the three groups ($P=0.27$). Only two milk-hypersensitive subjects had milk-specific IgE (>0.4 kU/l), while none of the other subjects had detectable amounts.

Discussion

In the present study, we observed immunologic changes, manifested in an overactive phagocytic process, during oral milk challenge in subjects clinically milk-nontolerant but with normal lactose tolerance test results. This substantiates the presence of milk hypersensitivity in adults.

Milk hypersensitivity is thought to be rare in adults, and only a few case reports (9-13) and studies (14-16) deal with that disorder. In contrast to previous reports, this study concentrated on chronic gastrointestinal symptoms of unknown cause in adults. The subjects in our study were selected from a small population, and nine out of 20 were milk-hypersensitive, whereas only five were lactose-intolerant. Therefore, it seems obvious that milk hypersensitivity is more common in the general population than previously reported. Moreover, the frequency of reported gastrointestinal reactions related to milk exceeds the prevalence of lactose intolerance. In Finland, 19% of the population report milk-related gastrointestinal reactions ($n=2152$, unpublished data from the Social Insurance Institution of Finland), while only about half of the 17% having lactase deficiency

experience reactions after one glass of milk (20, 21). This confirms that lactose may not cause all milk-related adverse reactions in adults (8).

The symptoms of milk hypersensitivity were found to be unspecific but similar to those observed in lactose intolerance. The reactions were reported to be delayed, appearing several days after milk consumption. The delay is also seen in reduced phagocyte activity during placebo challenge in the milk-hypersensitive group (Fig. 1), indicating that a 1-week milk-free diet may not have been long enough to dampen totally the allergic inflammation. Because of delayed symptoms, the interrelationship between symptoms and milk consumption may have been overlooked. Such chronic symptoms may have been misdiagnosed as lactose intolerance, irritable bowel syndrome, or psychologic intolerance.

It is presently understood that allergic sensitization to food allergens generally occurs during the first 2 years of age, often disappearing thereafter. However, sensitization to inhalant allergens generally occurs after 1–2 years of age. Milk-hypersensitive children do not form a homogeneous group: some of them have milk-specific IgE, but others do not. Some recover, but others develop asthma and other atopic disorders later in life (22, 23). Two out of nine of our adult subjects had elevated milk-specific IgE, and only one was atopic. This may indicate, firstly, that milk-hypersensitive children may "outgrow" to an adult form of milk hypersensitivity which seems to be less often IgE-mediated. Secondly, the clinical characterization of milk hypersensitivity in the adult population may differ completely from that in infancy. In order to ascertain the frequency of milk hypersensitivity in adults and particularly the frequency in atopic adults, larger-scale population studies are needed. The present study indicates that the tools currently available to detect such an adult population may be of poor diagnostic accuracy. To conclude, our results suggest that milk hypersensitivity in adults may be a key factor in many poorly defined gastrointestinal disorders.

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