

Usefulness of Measurement of Antibodies in Serum in Diagnosis of Sensitivity to Cow Milk and Soy Proteins in Early Childhood

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A noteworthy feature of this study is that comparisons were made between specific, sensitive, quantitative measurements of serum antibodies to food proteins and objective appraisal of clinical manifestations by double-blind food challenges. Over 50 children, 4-30 months of age, with suspicious histories of adverse reactions to cow milk or soy products were investigated. Levels of serum antibodies to cow-milk proteins were clearly higher in children with adverse reactions to milk, confirmed by blind challenge; there was no overlap with the lower levels of serum antibodies in children without confirmed reactions. Findings with serial determinations of serum antibodies to cow milk in selected cases are also presented.

The levels of serum antibodies evoked by cow milk and soy formulae fed from birth until 4 months of age were similar. The levels of serum antibodies to soy protein in children with and without adverse reactions to soy products were not definitive.

The bearing of these data on the comparative "antigenicity" of cow milk and soy products and the distinction between asymptomatic and clinically significant, symptomatic, sensitivity are discussed.

Key words: diagnosis; milk sensitivity; serum antibodies; soy sensitivity.

Accepted for publication 14 October 1979

In a previous paper (16) data were presented which indicated that measurement of serum antibodies may prove more useful in diagnosis of food sensitivity: 1) if the distinction between the mere presence of detectable antibodies in serum and the quantitative level was observed, and 2) if precise laboratory measurements were compared more carefully with equally accurate clinical appraisal of histories of adverse reactions to foods.

In the present study the levels of serum antibodies to cow-milk proteins were determined quantitatively in children less than 3

years of age who were suspected of reactions to cow milk. Double-blind challenges with cow milk were employed to accurately separate those with confirmable reactions from those without, for comparison with quantitative levels of serum antibodies.

In addition, some illustrative cases are given to show the usefulness of serial determinations of serum antibodies for extending knowledge of immunologic reactions to foods.

Because concern has been unduly aroused (8) about the "antigenicity" of soy protein products commonly used as substitutes for

cow milk in cases of milk sensitivity, some pertinent findings from our investigations are presented.

SUBJECTS

The children studied were 4–30 months of age. Except for a few, they were enrolled in a comprehensive study of food sensitivity in progress at the National Jewish Hospital and Research Center, which is approved by the Committee on Studies Involving Humans (2, 15). The children were derived from inpatient and ambulatory populations on the basis of histories of adverse reactions to cow milk or soy products.

PROCEDURES

Blind food challenges and other evaluations were carried out by admission to a Special Care Unit under continuous supervision of a staff trained for scientific observations, as described in detail in previous reports (2, 15).

Skin tests for detection of reaginic sensitization were performed with 1:20 w/v concentrations of verified extracts of cow milk and soybean, using the puncture technique. Earlier papers give the specifications of the extracts and details of technique (1, 2, 3, 15).

METHOD

Antibodies to cow milk and soy proteins in sera were measured with the antigen-binding procedure of Farr as described in detail in a previous paper (16).

The cow-milk proteins used as antigens were obtained from commercial sources (15). Bovine serum albumin (BSA), casein (CAS), alpha-lactalbumin (ALA), and beta-lactoglobulin (BLG) were used without further purification. The bovine gamma-globulin (BGG) was purified by passage through a DEAE-cellulose column.

The soy protein used as antigen was Edi-Pro A*, a soy protein isolate (SOY) widely used in preparation of soy formulae for infant feeding;

the sample was kindly supplied by the Ross Laboratories, Columbus, Ohio. Labeling of antigens with ^{125}I was carried out essentially as previously described (16).

The quantity of total specific antibody in serum is expressed in terms of the percent of ^{125}I -labeled antigen provided in the assay which was bound by 1:10 dilution of serum. The percent binding of the individual cow-milk proteins are presented in the Tables and also the sum of their bindings as an "Additive" value is included to simplify comparisons.

The discrimination of this antigen-binding assay for specific serum antibodies toward cow milk and soy proteins was demonstrated by the finding that no binding of any of these antigens occurred with sera from seven infants fed exclusively at the breast for 4 months.

RESULTS

Forty-one children, 4–30 months of age, had histories suspicious of adverse reactions to cow milk. Double-blind challenge with cow milk revealed that the suspicions were confirmed in 11 by definite adverse reactions; in 30 the suspicions were not confirmed by the challenges and cow milk was restored to the diets without adverse reactions.

The data concerning the 30 subjects without reactions in double-blind challenges are presented in Table I. The ages ranged from 4 to 30 months with a mean of 16 months. Puncture skin test with cow-milk extract 1:20 w/v was negative in all but one with a minimal significant net wheal of 3 mm. Binding of individual milk proteins by serum was greatest for BSA and CAS but the mean Additive binding (sum of the individual values) was only 48%, and the maximum Additive binding was 122%.

The data concerning the 11 subjects who exhibited adverse reactions to cow milk in double-blind challenges are presented in Table 2. The mean and range of ages were essentially the same as for the non-reactive group in Table 1, namely 16 months with a range of 5–30 months. The greatest binding by

serum was again with BSA and CAS, and the mean Additive binding of 248% was considerably greater than found for the non-reactors in Table 1. Furthermore the range of Additive bindings of 162-308% did not overlap with the upper limit of 122% in the range of Additive bindings of the nonreactors. Puncture skin test with cow-milk extract 1:20 w/v evoked significantly positive wheal re-

sponses in 5/8 of those in whom it was performed.

Serum for measurement of antibodies to cow-milk proteins could be obtained before and after milk challenge in 13 of the 41 subjects; the data are shown in Table 3. As all those who exhibited adverse reactions in blind milk challenges had elevated levels of antibodies to cow-milk proteins in serum before

Table 1

Antibodies to cow-milk proteins in sera of subjects 4-30 months of age without reaction to milk challenge

Age (months)	Puncture skin test*	Antigen bound by serum 1:10 (%)					
		(mm wheal)	BSA	CAS	ALA	BLG	BGG
4	0	0	7	0	0	0	7
4	0	0	0	2	3	0	5
6	0	0	26	8	0	0	34
6	0	5	15	3	2	0	25
6	0	3	18	3	0	0	24
6	0	4	23	0	0	0	27
7	0	5	31	3	4	0	43
8	0	37	37	15	6	27	122
11	0	30	48	4	6	11	99
11	0	13	48	0	8	12	81
13	0	8	33	5	5	0	51
14	0	5	8	4	4	0	21
14	0	10	31	14	2	0	57
15	0	3	27	0	0	0	30
18	0	6	8	8	3	14	39
18	0	6	9	2	0	0	17
18	0	3	15	0	4	0	22
21	0	49	14	14	3	15	95
21	0	1	6	0	0	0	7
21	0	22	20	8	3	15	68
24	0	7	25	3	2	2	39
24	0	37	53	2	2	17	111
24	0	34	12	0	0	16	62
24	0	14	16	16	2	1	49
26	0	57	32	1	9	2	101
26	3	33	15	0	1	7	56
27	0	22	36	6	5	21	90
28	0	7	6	0	0	0	13
30	0	6	3	0	0	0	9
30	0	1	10	1	0	34	46
No. 30							
Mean 16.8		14	21	4	3	7	48
s.d. 8.5		16	14	5	3	9	34.2
Range 4-30		0-57	0-53	0-16	0-6	0-34	5-122

*With cow-milk extract 1:20 w/v.

Table 2

Antibodies to cow-milk proteins in sera of subjects 5-30 months of age with reaction to milk challenge

Age months	Puncture skin test* (mm wheal)	Antigen bound by serum 1:10 (%)*†						Type reaction
		BSA	CAS	ALA	BLG	BGG	Additive	
12	6	88	67	59	54	9	277	Reaginic
6	11	99	45	54	4	0	202	Reaginic
25	3	96	48	16	10	27	197	Reaginic
5	0	100	40	65	34	55	293	Nonreaginic
10	0	25	84	27	37	70	240	Nonreaginic
15	ND	100	40	42	24	61	267	Nonreaginic
18	13	90	39	24	9	0	162	Reaginic
6	0	72	69	60	27	53	281	Nonreaginic
28	9	73	73	10	13	26	195	Reaginic
21	ND	30	84	60	33	97	304	Reaginic
30	ND	100	60	64	24	60	308	Reaginic
No. 11								
Mean 16		79	59	44	25	42	248	
s.d. 9		28	18	21	15	31	51	
range 5-30		25-100	39-84	10-65	4-54	0-97	162-308	

*With cow-milk extract 1:20 w/v.

†Antibody content of sera obtained before milk challenge.

N.D. = Not Done.

Table 3

Effect of milk challenge on level of antibodies to milk proteins in subjects 5-30 months of age

Age (months)	Puncture skin test* (mm wheal)	Milk challenge	Milk proteins bound by serum 1:10 (additive percentages)				
			Before challenge	After challenge	Interval (weeks)	Difference	Difference Before
<i>Serum antibodies elevated before challenge</i>							
5	0	+	293	310	3	17	.05
18	13	+	162	130	12	- 32	-.20
28	9	+	195	192	6	- 3	-.02
<i>Serum antibodies not elevated before challenge†</i>							
14	0	0	51	66	3	11	.21
15	0	0	30	130	4	100	3.33
18	0	0	17	40	3	23	1.35
21	0	0	7	70	4	63	9.00
21	0	0	95	67	4	- 28	-.29
15	0	0	37	29	13	- 8	-.21
26	0	0	56	41	5	- 15	-.26
26	0	0	101	169	4	68	.67
28	0	0	13	149	4	136	10.45
30	0	0	10	4	4	- 6	-.60

*With cow-milk extract 1:20 w/v.

†Milk added to diet after milk challenge found to be negative.

challenge, while those without reactions did not, the data are grouped accordingly in Table 3. The elevated levels of antibodies present before challenge in the three subjects who were found to exhibit adverse reactions to milk challenge did not rise significantly in the weeks after challenge. With the 10 subjects who did not react to milk challenge and who did not have elevated antibodies to milk proteins in the sera before challenge, the serum antibodies were not affected consistently by milk challenge. Appreciable increases (3–10-fold) were observed in only three of these 10 in the ensuing weeks.

The following results pertain to the usefulness of serial determinations of serum antibodies. In Table 4 are presented serial measurements of antibodies to cow-milk proteins in two subjects in late infancy who had milk eliminated from their diets for many months before being restored. In Case 1 no

serum antibody response was evident and the serum levels of antibodies to cow-milk proteins remained low. In contrast, with Case 2 there was a prompt increase in levels of serum antibodies, especially in antibodies to BGG. In neither subject did the milk challenge produce an adverse reaction, although histories of adverse reactions to cow milk had been obtained in both.

Table 5 provides serial determinations of serum antibodies to cow-milk proteins in an infant so sensitive to cow milk that urticaria was produced by antigenic material secreted in the mother's milk when she was drinking cow milk. Breast feeding was supplemented with a small amount of cow-milk product in nursery at birth and then the infant was breast fed exclusively. At 7 months of age urticaria developed after nursing, and the infant showed a 10-mm wheal to puncture skin test with cow-milk extract 1:20 w/v; mother's skin test was

Table 4

Effect of milk challenge on serum antibodies after prolonged elimination from the diet

	Antigen bound by serum 1:10 (%)					
	BSA	CAS	ALA	BLG	BGG	Additive
<i>Case 1—15 months of age</i>						
Milk eliminated 14 months	7	25	3	2	2	39
Milk challenge negative						
Milk in diet 3 months	8	16	2	5	0	29
Milk in diet 5 months	5	11	0	0	0	16
<i>Case 2—15 months of age</i>						
Milk eliminated 13 months	3	27	0	0	0	30
Milk challenge negative						
Milk in diet 1 week	13	34	0	0	73	120
Milk in diet 4 weeks	16	40	8	0	66	130
Milk in diet 3 months	11	29	10	7	30	87

negative. If the mother drank 1 glass of cow milk a day, the infant exhibited no symptoms during breast feeding, but if increased to 3 glasses a day, the infant developed urticaria. Prior to cautious oral administration of cow milk directly to the infant, in an attempt at desensitization, the levels of serum antibodies to the milk proteins were in the lower limit of the range found in normal, cow-milk fed infants of the same age. There was a rapid increase to high levels of antibodies to each of the milk proteins when milk was gradually increased orally. Although no symptoms or any evidence of enteropathy appeared, the attempt at desensitization was discontinued because of the possibility that with high levels of antibodies to milk proteins, injurious immune complexes could be formed. Later the levels of antibodies decreased but the Additive value was still elevated for this age. The rise and decline of antibodies to BGG appeared to reflect the variation in milk intake

most closely. In spite of breast feeding exclusively for 7 months, the serum antibody response to small amounts of milk introduced orally at 7½ months of age was much greater than we have found in normal infants fed customary amounts of cow milk from birth.

Among the children under study were some who had been fed soy products, with or without adverse reactions, thereby affording an opportunity to gather data on the significance of serum antibodies to soy protein. Simultaneously a separate study was in progress regarding serum antibodies to cow milk and soy proteins in normal infants fed milk and soy products from birth, which provided data for comparison with the findings in the subjects of the present study.

As can be seen in Table 6, normal infants fed either cow milk or soy formula from birth for nearly 4 months acquired serum antibodies specifically to the corresponding proteins in each formula. When fed a formula containing

Table 5

Serum antibodies to cow-milk proteins during attempted oral desensitization

		Antigen bound by serum 1:10 (%)					
Age (months)		BSA	CAS	ALA	BLG	BGG	Additive
7	Before attempted desens.*	3	15	2	1	0	21
7½	Began cow milk p.o. by gts						
10	Milk reached 49 gts q.d.	20	47	41	41	12	161
12	Milk reached 8 ml t.i.d.	84	75	72	39	84	354
13	Milk 90 ml t.i.d.	100	54	81	58	54	347
	Reduced milk to 10 gts. t.i.d.						
18	Only milk in other food	88	69	55	13	2	227
24	Only milk in other food	99	45	55	4	0	203
38	Only milk in other food	99	59	46	11	0	215

*No adverse reactions any time from amounts of milk given p.o.

both cow-milk and soy proteins, antibodies to both proteins appeared in the serum. At 4 months of age the antibody response to cow-milk proteins appeared to be significantly greater than to soy protein. The infants thrived with all three formulae and no adverse reactions occurred.

In Table 7 data are presented on serum antibodies to soy protein in older infants from the present study fed soy products at least 4 months. In the group who exhibited no adverse reactions to soy products, the level of serum antibodies to soy protein (mean binding

53%) was not significantly different from the level of antibodies to cow-milk proteins in the sera of infants of the same age period in Table 1 who were fed cow milk without adverse reactions (mean binding 48%).

Also the levels of serum antibodies to soy protein in children who had adverse reactions to a soy product were not higher than in those who did not. Because there was no evidence of reaginic sensitization to soy protein and serum antibodies to soy protein were not elevated, the adverse reactions may not have been due to an immunologic mechanism.

Table 6

Antibodies in serum to cow-milk proteins and soy protein in normal infants fed various products from birth for 112 days without adverse reactions¹

Group	No.	Ages	Percent antigen bound by serum 1:10					
			Soy			Additive milk proteins		
			Mean	s.d.	Range	Mean	s.d.	Range
Cow milk formula ²	6	112				43	28	10-80
Soy formula ³	16	112	17	9	0-28			
Cow milk and soy ⁴	8	112	22 ⁵	11	8-45	37 ⁵	16	12-59

¹ Excerpt of data obtained from a collaborative study with Dr. S. J. Fomon, Department of Pediatrics, University of Iowa Medical School, Iowa City, Iowa, from normal infants in his study of nutritional adequacy of various infant foods. A report of the complete data from our collaborative study of serum antibodies to cow milk and soy proteins is in preparation.

² 1.5 g protein per 100 ml.

³ 1.5 g protein per 100 ml (soy protein isolate-Edipro A).

⁴ 1.5 g protein per 100 ml: 73% from cow milk, 27% from a soy protein isolate-Edipro A.

⁵ Means are significantly different, $P < 0.05$.

Table 7

Antibodies to soy protein in sera in relation to adverse reactions to soy products

Group (No.)	Ages (months)		Soy protein bound by serum 1:10 (%)		
	Mean	Range	Mean	s.d.	Range
No reactions (8) ¹	15	6-24	53	25	17-100
Reactions (4) ²	14	5-30	31	30	12-76

¹ A soy product fed 4 months or more.

² Reactions were confirmed by double-blind challenge with a soy product. All reactions were non-reaginic (negative skin test) and manifest by diarrhea.

DISCUSSION

Many studies have been made of antibodies to cow-milk proteins in the serum and all reports agree on their regular detection in sera of nearly all infants and children fed cow milk (12, 20, 23). The conclusion has generally been drawn that serum antibodies to cow-milk protein have little or no diagnostic usefulness, except in rare instances of extreme elevation (9, 10, 20). Some of the methods of antibody assay employed did not yield quantitative measurements or were relatively insensitive (18). Usually the subjects were not precisely classified as to symptomatic clinical sensitivity to cow milk, that is, whether present or not.

Consequently, it seemed desirable to re-examine the diagnostic usefulness of measurement of serum antibodies to cow-milk proteins taking the foregoing considerations into account. This was done by 1) use of a specific, sensitive, quantitative assay for antibodies in serum, and 2) precise, objective determination of the presence or absence of clinically significant, symptomatic sensitivity to cow milk by means of double-blind challenges with milk.

Sera of all children with suspicious histories of reactions to cow milk confirmed by double-blind challenge with milk (Table 2) had higher levels of antibodies to cow-milk proteins than the children without reactions confirmed by challenge (Table 1). None of the children without reactions to cow milk confirmed by blind challenges (Table 1) had levels of serum antibodies to milk proteins within the higher range of values found in those with reactions to milk.

However, we have also observed another group of eight children, 12–28 months of age, who were found to have elevated levels of serum antibodies to cow-milk proteins (Additive binding 165–273%), which are within the elevated range shown in Table 2 for children with confirmed reactions to cow milk. None of these eight children reacted to milk in blind challenges. Histories of diarrhea were obtained in six of these children and the

diarrhea persisted for a short period after admission to the Special Care Unit. However, the diarrhea soon ceased when milk was added to the diet, after finding no reaction was evoked by milk challenge. Diarrhea did not recur during prolonged observations in the Unit. The etiology of the diarrhea was not discovered by extensive investigation. The other two children in this group had sensitivity reactions to other foods confirmed by blind challenges.

Therefore, although higher levels of serum antibodies to cow-milk proteins were observed in all children with confirmed reactions to milk (Table 2), a reaction to milk will not necessarily be evoked in blind challenge in all children with elevated levels of serum antibodies. Elevated levels do suggest intestinal disturbance from sensitivity to milk or another food or from some other disorder may be present. In contrast, levels in the lower range (Table 1) provide substantial evidence that suspicious histories of reactions to cow milk will not be confirmed by blind challenges. We have come to use elevated levels of serum antibodies to cow-milk proteins in infancy and early childhood as a warning of an underlying intestinal disturbance, either from food sensitivity or some other disorder. Among other uncommon sources of greatly elevated serum antibodies to milk proteins are selective IgA deficiency and aspiration of milk into the lungs, not represented in the subjects of the present study, but well documented by others (4, 10, 13, 14).

In the present study the five major proteins in cow milk were used as antigens to observe the individual antibody responses. The greatest responses were almost always to BSA and CAS in both those with and those without reactions to cow milk, even though BSA constitutes only 1% while CAS is 84% of protein in cow milk (Tables 1, 2). In serial determinations, the levels of serum antibodies to BGG appeared to reflect the effect of acute addition or withdrawal of dietary milk most sensitively (Tables 4, 5). For diagnostic purposes, assay for serum antibodies to milk

using one radiolabeled antigen, BSA or CAS, may suffice, rather than the Additive binding of five milk proteins.

Obviously a serum specimen obtained after prolonged complete elimination of cow milk, as when a soy product has been substituted, may not reveal an elevated level of antibodies to cow-milk proteins even if the individual is sensitized to milk. Interpretation of the assay results must take this into account. After a milk challenge, a booster effect may cause the level of serum antibodies to rise whether a reaction occurs or not (Table 3).

Examples of the application of serial determinations of serum antibodies to cow-milk proteins to elucidate immunologic consequences of elimination and addition of milk in sensitized persons are shown in Tables 4 and 5. The data from Case 2 in Table 4 and from the patient in Table 5 indicate that early and prolonged elimination of milk from the diet may not preclude a brisk antibody response when it is ultimately added again in late infancy. The marked elevation of serum antibodies in the patient in Table 5 suggests attempts at oral desensitization may not be prudent even though the reagin-mediated reactions may be lessened.

The fact that serum antibodies to food proteins are detectable in nearly all infants and young children has led to the commonly held view that such antibodies are "natural" or "physiologic". This should not be construed to mean that the higher levels of serum antibodies to food proteins may not be indicative of pathologic conditions, as has already been discussed. That all individuals have glucose in the blood does not negate the significance of exceptionally high levels. The formation of immune complexes when individuals with high levels of serum antibodies to milk protein ingest milk, and their potential for pathologic effects, is currently being studied (6).

The findings and conclusions of the present study regarding diagnostic usefulness of assay of serum antibodies to cow-milk protein pertains particularly to individuals 4-30 months of age (Tables 1, 2); extrapolation to

the period up to 4 months of age may be reasonable in principle but similar data in this age period are needed for substantiation.

The significance of serum antibodies to soy protein (Tables 6 and 7) must be appraised according to the same criteria that have been applied to serum antibodies to cow-milk protein. This means correlation of accurate, quantitative laboratory measurements with precise clinical diagnoses determined by blind challenges (1, 2, 3, 15, 16). In addition, an adverse reaction is not necessarily based on an immunologic mechanism. Furthermore, the distinction between asymptomatic sensitization without clinical significance and clinically symptomatic sensitivity must be recognized (17). Failure to abide by these fundamental considerations may lead to the same sort of muddled comments on antigenicity of soy proteins (8) that have troubled physicians about cow milk antigenicity and its clinical significance.

As could have been predicted of any food protein, soy protein was found years ago to evoke antibody production in man and animals (11, 22). At the same time, soy protein was shown to be weakly antigenic in man and animals compared to cow-milk protein and the antigenicity of soy was greatly reduced by heat processing of soy products (5, 11, 21, 22). Although reaginic sensitization could be produced by soy protein in man, rarely was clinically significant, symptomatic sensitivity observed (11, 22). Among the relatively few adverse reactions to soy products reported (24), seldom has evidence for an immunologic basis been provided, and the adverse reactions presented in Table 7 had negative skin tests and no increase in serum antibodies to soy. Soy products have been shown to produce an adverse reaction by chemical toxicity of a constituent, the soy lectin (7).

Thus, although soy protein is naturally antigenic, the degree and the sort of sensitization appears to be such that the incidence of clinically significant, symptomatic immunologic reactions among infants fed soy may be considerably less than the incidence of

clinically significant, symptomatic immunologic reactions among infants consuming cow milk.

Actually, sensitization through inhalation of soy flour or pollen and ensuing respiratory reactions may be as important, especially in later childhood and adults (19). Certainly the true role of soy products in sensitivity and other disorders should be ascertained by sober, scientific investigation before judgment is passed on the use of soy products in human nutrition.

ACKNOWLEDGEMENT

Special appreciation is extended to the nursing staff of the Special Care Unit in which children were kept for observations during double-blind challenges.

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