
Natural history of severe reactions to foods in young children

Nine children with very severe adverse reactions to foods during the first 2 years of life were followed to determine the subsequent course of their reactions. Cautious challenges were given in these children over a period of time. Three of nine children can tolerate the offending food in usual portions; four of nine can tolerate small amounts of the offending food; and two children continue to have reactions to small amounts of the offending food. At some time each of these children have exhibited significant positive wheal and flare reactions when skin tested with extracts of the offending food. This study demonstrates that some children with severe reactions to foods may lose their frightening reactivity to foods over time. Very careful challenges in these patients are thus justified to save families from prolonged anxiety about accidental ingestion, which inevitably occurs. (J PEDIATR 1985;107:676-680)

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AS THE EVALUATION of patients with objectively proved food sensitivity has progressed, it has become clear that children's reactivity to foods often changes as they grow older.^{1,2} We have seen a number of children with very severe, often anaphylactic, reactions to foods. Concern over what might occur on accidental ingestion of offending foods has prompted us to maintain our contact with the children and to challenge them very cautiously with small amounts of the offending food over a number of years. We have been gratified to find that these children regularly lose their frightening reactivity to foods.

METHODS

Nine children from the food sensitivity studies³⁻⁵ at National Jewish Hospital and Research Center/National Asthma Center had very severe adverse reactions to foods before they were referred for evaluation, and have been

followed for 3 to 9 years since their initial reactions. Each of these children had severe symptoms on one or more occasions to milk, egg, or soy (Table). No other foods in the diet were incriminated. For purposes of this report, severe reactions were those requiring prompt medical intervention, and included laryngeal edema, wheezing, paroxysmal cough, diarrhea or vomiting leading to dehydration requiring fluid replacement, shock documented by fall in blood pressure, angioedema, and generalized urticaria. Anaphylaxis is defined as respiratory symptoms (wheezing, laryngeal edema), hypotension (either measured or considered likely by the child's appearance), and urticaria.

Double-blind food challenges, beginning with very small quantities of food, were used to determine the patients' reactivity after they were identified by a history of reaction. The procedures were slight modifications of previously published descriptions of double-blind food challenges.³⁻⁵ The foods were used in dry form (powdered milk, powdered egg, or soy flour) or liquid form (whole cow milk or soy formula) and were placed in a formula or food the child was already taking. The initial quantity for challenge was one tenth or less of the smallest quantity thought to have produced the original reaction. The quantities noted in the Table are the single-dose amounts that produced symptoms, and do not include incremental challenges

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given earlier the same day. Each reaction occurred within 15 to 120 minutes (mean 45 minutes) of challenge. The challenge was stopped at the first sign of objective symptoms. In the nine children, 23 challenges were administered blindly under observation in the Pediatric Special Care Unit of National Jewish Hospital. (This unit also serves as an intensive care unit for children with severe asthma, and is completely equipped and staffed to undertake emergency resuscitative care.) Challenges denoted as "small" or "usual" quantities were administered openly at home by the parents. Twenty-one challenges were administered openly outside the hospital; those in patients 2 and 3 were carried out without consulting us.

Skin testing by the puncture technique, with a 1:20 wt/vol concentration of food extract, was also carried out according to a method long used at this institution.^{6,7} This included verification of extracts to show that they detected antibody in sensitized children and did not produce reactions in children who were not sensitized. The extracts used in this study were given to other children in the same age group and did not produce nonspecific reactions. A wheal ≥ 3 mm in diameter, compared with reaction to the diluent control, indicated significant immunologic sensitization.

Two children (patients 3 and 4) were also being followed by a pediatric gastroenterologist, who performed a small-bowel biopsy to confirm protein-induced enteropathy. Detailed studies of these biopsies have been reported.⁸

RESULTS

All but one child (patient 7) experienced a first reaction before 12 months of age. (The initial reports for each child included descriptions of symptoms noted and treatment administered by the referring physician who had seen the children at the time of these reactions.) Reactions to historically incriminated foods were confirmed by the initial challenge under observation. The foods producing reactions were milk (all nine patients), egg (two), and soy (one); three of the children reacted to more than one food.

Symptoms noted in the clinical histories included laryngeal edema, wheezing, generalized urticaria, vomiting, diarrhea (with marked fluid loss), and circulatory collapse. Epinephrine was administered to six of the children at the time of the initial reaction; on one occasion each, three (patients 3, 4, and 8) required intravenous fluids to reverse circulatory collapse.

Subsequent challenges, repeated over a number of years, resulted in fewer reactions and gradual tolerance of larger amounts of the offending food. At this time, three of the nine children (patients 2, 3, and 4) are able to tolerate the originally offending food in usual and customary quanti-

ties; and four (patients 1, 5, 8, and 9) can tolerate large enough quantities so that they may consume foods made with the offender or small amounts of the offender itself. Two children (patients 6 and 7) continue to have reactions to small amounts of milk when it is accidentally ingested. In patient 6, neither of the two most recent reactions, at ages 42 and 54 months, produced the marked angioedema and severe wheezing noted after earlier exposures. At 60 months, patient 7 was given 2.5 ml milk openly in a pediatric clinic and developed pallor and vomiting; a few days later he ingested about 20 ml accidentally and had generalized symptoms.

Patient 3 is notable because at age 11 months she seemed to tolerate soy, which was not placed in the diet regularly; then 2 months later (age 13 months) she vomited after soy ingestion. Subsequently soy was tolerated in usual quantities. These observations were made in the special care unit and were reproduced on 3 consecutive days.

The presentation and challenge in patient 4 was different from those of the others. At 2 months of age he was admitted to a local hospital with persistent diarrhea and mild dehydration, which his mother thought was caused by cow milk. The house staff ordered a cow milk formula, and shortly after the first feeding he had marked vomiting, worsened dehydration, and fall in blood pressure; within 2 hours he had a massive watery stool. He recovered promptly after intravenously administered rehydration. Within 24 hours he underwent a small-bowel biopsy, which showed a flattened jejunal mucosal surface with almost no recognizable villi and a marked increase in inflammatory cell infiltrate⁸; these changes were compatible with cow milk protein enteropathy. His mother refused to allow skin tests or subsequent challenges. He was lost to ongoing evaluation until he appeared in the clinic at 36 months, accompanied by his grandmother, who reported that he had been drinking cow milk for many months with no problems. He appeared quite healthy, with normal growth.

Skin tests. Eight of the nine children underwent skin testing at the time of their initial evaluation at NJHRC/NAC. Six of the eight underwent sequential skin testing over a period of years. Six children had a positive reaction to puncture test with an extract of the offending food at the time of initial referral. Patients 8 and 9 (monozygotic twins) had consumed only small amounts of milk in their entire lives. Patient 8, who had the more marked clinical reaction, had a borderline skin reaction to an intradermal skin test at 1:1000 wt/vol; his sibling had no reaction to testing with both puncture and intradermal tests. Seven months later, without any further known exposure to milk and before the 7-month challenges, both children had a positive reaction to puncture skin test with milk. None of

Table. Onset, course, and skin test results in children with severe reactions to foods

Patient	Initial reaction*			Challenge			Skin test†		
	Age (mo)	Food	Symptoms	Age (mo)	Quantity of food	Symptoms	Age (mo)	Food	Wheal diameter (mm)
1	4	Milk	Laryngeal edema, urticaria, wheezing	7	2 ml	Vomiting	7	Milk	10
				11	10 ml	None			
				56	Small amount	None	39	Milk	5
				108	Small amount	None	44	Milk	5
2	1	Milk	Urticaria, "anaphylaxis"	47	750 mg	Eczema, rhinitis, urticaria, wheezing	47	Milk	9
									12
				53	2 ml	Wheezing	53	Milk	
				57	500 mg	Urticaria			11
	15	Milk		70	10 ml	Urticaria	70	Milk	8
				96	Small amount	None	96	Milk	
				99	Usual quantity	None			
				46	10 mg	Rhinitis, wheezing	46	Egg	4
	12	Egg	"Anaphylaxis"	56	200 mg	Urticaria	56	Egg	6
				70	3000 mg	Urticaria, wheezing	70	Egg	10
				96	Small amount	None	96	Egg	9
				99	Usual amount	None			
3	2	Milk	Diarrhea, dehydration, vomiting	9	5 gm	Vomiting	6	Milk	9‡
							9	Milk	3
				15	8 gm	Urticaria, diarrhea	13	Milk	3
				34	Small amount	None	34	Milk	0
	2	Soy	Diarrhea, dehydration, vomiting	50	Usual amount	None			
				6	Formula 10 ml	Vomiting, pallor	6	Soy	3‡
				8	Flour 500 mg	Vomiting			
							9	Soy	3
				13	Usual amount	None	13	Soy	3
				15	Formula 180 ml	Vomiting			
				16	Formula 120 ml	None			
				34	Small amount	None	34	Soy	0
4	2	Milk (in hospital)	Dehydration, shock, vomiting	50	Usual amount	None			
				36	Usual amount	None		ND	
5	1	Milk	Angioedema, cough, urticaria	26	30 ml	Rhinitis, sneezing, urticaria	22	Milk	7
	6	Milk	Angioedema, laryngeal edema, urticaria	32	Small amount	None			

Milligram quantities are of dried food.

ND, not done.

*Adverse reactions to food before initial visit to NJHRC/NAC.

†Puncture skin test except as noted.

‡Intradermal skin test.

§Child became upset and vomited as challenge progressed.

the eight children had symptoms during the skin testing procedure.

DISCUSSION

The course in these children offers some comfort to parents, pediatricians, and allergists caring for children who have experienced severe adverse reactions to foods. This experience should not, however, be construed as promoting a casual or cavalier attitude toward challenges in children with this type of history. We feel fortunate that

we have never seen (nor had reported to us) a fatal reaction to a food in a young child.

These data should encourage careful challenges of children with histories of severe reactions, at suitable intervals and using small quantities to initiate the challenge. The procedure should always be performed in a setting where emergency treatment can be promptly provided, for example, intensive care units, emergency rooms, and outpatient clinics with properly equipped treatment rooms, staffed with personnel experienced in treating

Table—Cont'd

Patient	Initial reaction*			Challenge			Skin test†		
	Age (mo)	Food	Symptoms	Age (mo)	Quantity of food	Symptoms	Age (mo)	Food	Wheal diameter (mm)
6	10	Milk	Angioedema, urticaria, wheezing	26	5 ml	Angioedema, urticaria	26	Milk	3
				30	1 Drop (accidental)	Urticaria, wheezing			
				42	1 to 2 ml (accidental)	Cough, itch, wheezing			
				54	Food with whey (accidental)	Pharyngeal itch			
7	1	Milk	Rhinitis, sneezing, omiting, dehydration	18	2 ml	Itch, rhinitis, sneezing	18	Milk	7
				26	60 ml	Rhinitis, urticaria, wheezing			10
				34	Cheese (accidental)	Sneezing, urticaria	37		
				60	Food with whey	None or itch	60		5
	14	Egg	Urticaria, cough, eczema		Milk 2.5 ml	Pharyngeal itch, vomiting		Egg	
					20 ml (accidental)	Angioedema, cough, diarrhea, vomiting, pallor, urticaria			
						Urticaria, wheezing, sneezing, itch			
8	6	Milk	Diarrhea, vomiting	17	20 ml	Urticaria, vomiting	18	Egg	7
							37	Egg	10
	8	Milk	Diarrhea, dehydration, shock, vomiting				60	Egg	7
9	6	Milk	Diarrhea, pallor, vomiting	41	8 gm	Contact urticaria only	8	Milk	3‡
				51	Increasing amounts in diet	None	17	Milk	4
							22	Milk	15
							34	Milk	9
							41	Milk	3
9	6	Milk	Diarrhea, pallor, vomiting	17	20 ml	Urticaria, vomiting	8	Milk	0
							17	Milk	3
							22	Milk	7
							34	Milk	4
9	6	Milk	Diarrhea, pallor, vomiting	41	5 gm	Vomiting§	41	Milk	5
				51	Increasing amounts in diet	None			

urgent cardiovascular and respiratory problems. Challenges in these youngsters should not be performed in physicians' offices. Such controlled challenges are far better than the accidental exposures that invariably occur as young children begin to spend time at the homes of friends, in day care settings, and at school. In one of our patients (patient 6), who has been too far away for us to supervise, accidental exposures to milk have caused the two most recent reactions (at ages 42 and 54 months).

An important point is illustrated by patient 3. At one time this child appeared to tolerate soy, but a subsequent ingestion produced vomiting; finally, the food was successfully tolerated. The mechanism of this sequence of reactions is unclear but may be related to a booster antibody response from the challenge preceding the reaction. Alter-

natively, more antigen could have been absorbed at the time of the reaction than when the food was tolerated, for some reason that is not apparent. Thus, even when the food does not appear to be producing symptoms any longer, cautious monitoring must continue for a time.

The conclusion from these experiences is similar to that from our studies in children with less severe reactions.³⁻⁵ When a blind challenge has yielded negative results, the food must be introduced openly in the diet for confirmation, preferably under supervision. In the highly reactive type of children we report, gradual liberalization of the diet should be undertaken only with suitable precautions. Once the food has been tolerated in a quantity that has practical application to the diet, the parents are instructed to give this amount to the child carefully at home. In less

severe cases than those we report, parents are allowed to increase the amounts incrementally (for milk the increments are usually 1 oz at a time). No effort has been made to give the child the offending food each day. For children such as those we describe, the incremental increase should also be carried out under observation (this advice is often not followed by parents).

Skin testing in these children revealed significant reactions over time, and the detectable skin sensitization persisted longer than the clinical reactivity, a finding observed previously.¹ The association of positive skin test results with reactions to the offending foods on ingestion strongly implicates an IgE-mediated mechanism. Recently Sampson and Jolie⁹ have used a sensitive assay to show significant elevations of plasma histamine following blind food challenges in some patients with atopic dermatitis, thus associating at least one of the known inflammatory mediators with food reactions *in vivo*.

Two of our patients had alterations in the small bowel mucosa after food challenges that produced clinical symptoms. These alterations suggest that more than one immunologic mechanism may be involved in the production of the symptoms. Data in the literature support the involvement of the immune system in the production of gastroenteropathies,^{10,11} but it has yet to be proved that the immune system is primarily responsible for the illness, rather than the possibility that the immunologic findings are secondary to pathogenic changes induced by nonimmunologic mechanisms.

The question has been raised concerning whether we might have "desensitized" these children in a similar manner to the desensitization that occurs in penicillin-sensitive patients given increasing doses of the antibiotic at short intervals. This possibility is not totally denied, but it seems unlikely because the children have not had the offending food in multiple doses each day. When the food was not consumed regularly, a subsequent ingestion did not produce more severe symptoms.

A likely hypothesis to explain these observations is that over time there are changes in the absorption and processing, both immunologic and nonimmunologic, of dietary proteins. Actually, an attempt was made to desensitize patient 1 when we first saw him at age 7 months. He was given a few milliliters of milk each day in very slightly increasing increments. Concurrently measurements were made of his circulating antibodies to cow milk proteins.¹² The challenge was discontinued when his antibody levels became quite elevated and we became concerned that

injurious immune complexes might be formed. During the subsequent years, he has never had a reaction as severe as the initial one, even when given milk after prolonged abstinence.

In conclusion, physicians caring for children exhibiting severe adverse reactions to foods are encouraged to undertake careful periodic challenges in these patients. It is arguably much safer to trigger a mild reaction under observation than to cope with a severe reaction in a nonmedical setting. It is very comforting to families when they are relieved of the burden of watching everything a child eats, for fear that it may contain proteins that could cause a severe reaction.

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