

Challenge confirmation of late-onset reactions to extensively hydrolyzed formulas in infants with multiple food protein intolerance

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Background: Many infants with cow's milk protein intolerance have adverse reactions to soy, casein and whey hydrolysate formula and to other foods. The recent development of Neocate, a hypoallergenic, nutritionally complete infant formula composed of individual amino acids and other nutrients, has enabled these infants to be stabilized.

Objective: We observed the effect of food challenges in infants with reported hypersensitivity to hypoallergenic formulas.

Methods: Eighteen infants (median age, 7½ months) were given Neocate formula for 2 months and then underwent a 7-day double-blind placebo-controlled challenge with the formula previously best tolerated.

Results: In 12 of the 18 infants irritability, vomiting, diarrhea, and/or eczema flares developed during the formula challenge. In two patients symptoms developed immediately, but in the remainder adverse reactions evolved within 7 days (range, 4 to 7 days). Adverse reactions were to soy formula (six patients), whey hydrolysate (two), and casein hydrolysate (four). When infants were 12 months of age, parents reported adverse reactions after the ingestion of other low allergen foods (median, six; from a panel of 10 such foods).

Conclusion: A group of infants with late-onset adverse reactions to soy, extensively hydrolyzed casein, and whey formulas and to other foods has been identified. Neocate formula proved to be an effective substitute formula for these patients. (*J ALLERGY CLIN IMMUNOL* 1995;96:386-94.)

Key words: Hypersensitivity, extensively hydrolyzed formulas, multiple food protein intolerance, infancy

Studies from our laboratory have described the clinical and immunologic features of cow's milk allergy (CMA) in infants and young children.¹ These investigations, based on objective challenges with cow's milk in a specialist clinic, identified three groups of patients² and described their immunologic features³⁻⁵ and the natural history of this disease.^{1,6-8} Other investigators have recognized a similar spectrum of intolerance to cow's milk proteins.^{9,10} In the first group, comprising

Abbreviations used

CMA: Cow's milk allergy
DBPC: Double-blind, placebo-controlled
SPT: Skin prick test

immediately reacting patients, symptoms of urticaria, eczema flares, wheezing, and anaphylaxis, or a combination of these, developed within minutes of ingestion of small volumes of cow's milk. In the intermediately reacting second group vomiting and/or diarrhea developed several hours after ingestion of moderate amounts of cow's milk. The third group of patients were late reactors who frequently tolerated normal volumes of cow's milk for up to 24 hours before eczema or gastrointestinal or asthmatic symptoms developed.^{1,2} Only the immediately reacting patients and patients with

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eczema in the third group showed evidence of IgE-type hypersensitivity to cow's milk proteins.^{1,3} In all patient groups the IgG anti-cow's milk antibody levels were low.³

As a group the late-reacting non-IgE-sensitized patients with CMA had elevated T-cell reactivity in vitro to milk proteins, reflected by enhanced leukocyte migration inhibition factor and interferon- γ production.^{4,5} Recently, Suomalainen et al.¹⁰ also described enhanced T-cell reactivity to milk proteins in vitro in non-IgE-sensitized patients with CMA.¹⁰

In our initial studies 47% and 22%, respectively, of our patients with CMA had slowly evolving adverse "late" reactions within several days, not only to cow's milk but also to soy milk and casein hydrolysate and to other foods (i.e., patients were intolerant to multiple food proteins).⁶ In the last decade we have identified 60 similar infants with late adverse reactions to these formulas, including whey hydrolysate (unpublished data). Some patients received a preparation containing individual amino acids¹¹ designed for adult use, but it was relatively poorly tolerated by infants. A nutritionally complete infant formula composed of individual amino acids, fat, carbohydrate, minerals, and vitamins (Neocate, Scientific Hospital Supplies, Liverpool, U.K.) has been well tolerated by our patients with hypersensitivity to multiple infant formulas.

This study describes the clinical features of 18 infants who clinically had late hypersensitivity reactions to multiple infant formulas, were stabilized by Neocate formula, and underwent double-blind placebo-controlled (DBPC) challenges with different soy-based and extensively hydrolyzed formulas. The effect of the subsequent introduction of a range of low-allergen foods to the diet of these infants was documented.

METHODS

Patients

Eighteen patients (11 boys, seven girls; median age, 7½ months; range, 3 to 14 months) with a history of adverse reactions after ingestion of cow's milk, soy milk, casein, and/or whey hydrolysate formulas were referred to us. The reasons for referral and the associated features noted on history or examination are shown in Table I. In summary, the major presenting features were (1) distressed behavior associated with varying degrees of vomiting, with or without diarrhea (patients 1, 3 to 9 and 12 to 15); (2) severe generalized eczema (patients 11, and 16 to 18); (3) protracted diarrhea (patient 2); and (4) growth failure (patients 5, 10, 16, and 18), which was associated with severe generalized eczema in two cases (patients 16 and 18).

Before referral, endoscopic biopsies of the upper and lower gastrointestinal tract were performed on nine patients (patients 1, 4 to 9, 12, and 13) in whom irritability was the prime reason for referral. Minor degrees of eosinophil and neutrophil infiltration of the esophagus (three cases), gastric antrum (one), and duodenum (one) were noted. Eight of the patients who underwent endoscopy had previously been treated with H₂-antagonists (five patients) and/or prokinetic agents (six), but irritability persisted. Findings of a duodenal biopsy on the infant with diarrhea alone (patient 2) were normal.

After referral patients underwent allergen skin prick tests (SPTs) with dietary and inhalant allergens, and serum total IgE and allergen-specific IgE antibodies were measured. Patients began receiving Neocate formula; in addition, patients with eczema were treated with flucloxacillin, topical betamethosone valerate ointment (0.02%), and acemetasone dipropionate ointment (for facial eczema only). Irritability, gastrointestinal symptoms, and eczema remitted within 2 weeks. A small number of foods (usually rice, potato, pumpkin, or zucchini) were sequentially added to the diet after week 2. Further reviews were undertaken at weeks 4 and 8.

Measurement of IgE antibodies

Before use of Neocate formula started, all patients underwent SPTs with dietary and inhalant allergens, and in 11 infants total serum IgE and allergen-specific antibodies were measured. The following allergen extracts and control solution were purchased from Dome-Holister-Stier (Spokane, Wash.): whole cow's milk, egg white, codfish, wheat, soy, peanut, *Dermatophagoides pteronyssinus* (house dust mite), *Lolium perenne* (rye-grass pollen). SPTs were performed by one of three specially trained allergy nurses. One drop each of the extract, control solution, and histamine were placed on the subject's skin, and the point of a blood lancet was passed through the drop to indent the skin but not cause bleeding. The size of the skin wheal elicited by the extracts was compared with that elicited by 1 mg/ml histamine acid phosphate and by a negative control solution. The size of the wheal elicited by the control solution was subtracted from that elicited by each allergen before the test score was given. The mean diameter (taken at right angles) of the wheal and pseudopodia elicited by the histamine was designated as 3, and reactions to the extracts were graded by reference as follows¹²: greater than 4, at least twice the area of histamine standard; 4, reaction varying from area equal to that of histamine standard up to twice the area of that standard; 3, from half the area of histamine standard up to the area of histamine; 2, from one fourth to half the area of histamine standard, up to the area of histamine; 1 from the control solution reaction to one fourth of the area of histamine standard. Total serum IgE, in international units per milliliter, was measured by radioimmunoassay (Kallestadt Diagnostics, Minn.), and allergen

TABLE I. Clinical features of patients

Patient No.	Age at presentation (mo)	Presenting symptoms							Skin test score*	RAST score†	Total IgE (IU/ml)
		Irritability	Vomiting	Diarrhea	Eczema	FTT	Other*				
1	5	++	++	-	-	-	-	-	NE	NE	
2	7	+	-	++	-	-	-	-	-	5	
3	3	++	++	-	-	-	-	-	NE	NE	
4	10	++	++	-	-	-	-	M = 3, E = 5	-	5	
5	7½	++	++	-	-	++	+	-	NE	NE	
6	3	++	-	+	-	-	-	-	NE	NE	
7	10	++	++	-	-	-	+	E = 3, P = 3, S = 3	E = 3, P = 3	142	
8	5	++	++	-	-	-	-	-	-	5	
9	7	++	++	-	-	-	-	-	NE	NE	
10	8	-	-	-	-	++	-	-	NE	NE	
11	6	-	-	-	++	-	-	M = 4, E = 5, P = 4, S = 2	M = 2, E = 3, P = 3, W = 3, S = 3	3710	
12	3	++	++	-	-	-	-	-	-	17	
13	8	++	+	++	-	-	-	-	M = 3, E = 3, W = 3, F = 2	41	
14	7½	++	++	-	+	-	-	-	-	6	
15	4	++	+	++	-	+	-	M = 5, E = 3	M = 2, E = 2	9	
16	12	-	+	+	++	++	-	M = 5, E = 5, P = 5	M = 3, E = 3, P = 3, W = 3	8900	
17	9	-	+	-	++	-	-	M = 3, E = 5, P = 5	M = 4, E = 2, P = 4, S = 2	890	
18	14	-	-	-	++	++	-	M = 4, E = 5, P = 5	M = 3, S = 2	82	

+, Minor symptoms; ++, major presenting symptoms; -, negative; E, egg; FTT, failure to thrive; M, milk; NE, not examined; P, peanut; S, soy; W, wheat.

*Includes rhinitis and cough.

†See text for details.

IgE antibodies to cow's milk, egg, wheat, peanut, codfish, *D. pteronyssinus*, and *L. perenne* were measured by an enzyme-labeled anti-IgE method (Kallestadt Diagnostics) and reported as a RAST score, from 0 to 4, according to the manufacturer's directions.

DBPC challenge procedure

Patients were ingesting Neocate formula for a median period of 14 weeks (8 to 28 weeks) before a DBPC challenge with either soy, casein hydrolysate, or whey hydrolysate formula was performed. Parents selected the challenge formula that had previously caused the least adverse effect before referral.

Fig. 1 shows the design of the DBPC challenge procedure together with volume and protein content of the formulas used for challenge. The sequence of challenge was randomized by a computer program. The challenge periods were preceded by a run-in period of 1 week and separated by a washout period of 1 week. The control formula was prepared from Neocate formula alone. The active test formula was diluted in Neocate formula such that on day 1 active formula was one tenth

of the volume taken, on day 2 active formula was one fifth of the volume taken, and on days 3 to 7 active formula was one third of the total volume taken. Thus from day 3 to day 7 patients consumed a median volume of 300 ml of test formula mixed with 600 ml of Neocate formula (i.e., a total volume of 900 ml of the challenge formula). The active and control formula preparations were dispensed in identical coded sachets of powder and when prepared for ingestion could not be distinguished by taste, appearance, or smell. In weeks 2 and 4 of the study, the challenge formula was given in our department for the first 2 days, irrespective of whether it was the active or placebo limb of the investigation, but subsequent increment in dose was administered at home (days 3 to 7). Patients were reviewed at weekly intervals. For the 4-week study period other aspects of the diet remained unchanged.

Assessment of response to DBPC challenge procedure

Two methods were used to measure the effect of challenge during the 28-day study period.

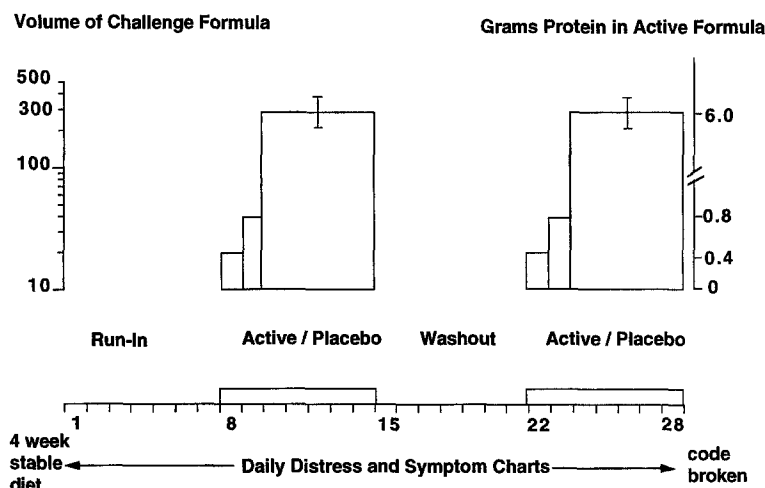


FIG. 1. Design of DBPC challenge. Vertical axis at *left* indicates volume of challenge protein, and axis at *right* indicates mass of challenge protein in the active formula. *Height* of the histogram represents the volume and amount of protein, and *width* represents the days on which challenges were given. *Lower part* of the figure indicates the time during which daily distress and symptom charts were completed.

1. Distressed behavior (i.e., crying and fussing) was recorded on a 24-hour cry/distress chart previously validated against an objective measure of distress.^{13,14}
2. Daily symptoms of rhinorrhea, vomiting, stool frequency, skin rashes, coughing, wheezing, and distressed behavior were recorded on daily diary score cards. These cards have been used to score nonimmediate adverse reactions to cow's milk in other studies.^{4,5}

At the end of the 28-day study period, an assessment of the effect of challenge was made on the basis of: (1) parental assessment (i.e., parents were asked whether there were any adverse effects of either test formula, the nature of these adverse effects, and the code formula responsible for them), (2) duration of 24-hour infant cry/distress scores for the days active formula was received versus days control formula was received and (3) daily symptom scores for the days active formula was received versus the days control formula was received. After these assessments were completed, the code was broken. Infants who tolerated the active test formula were weaned fully on it, but those with persistent intolerance resumed taking Neocate formula.

Patients were regarded as having persistent intolerance to the active test formula if two of the three criterion responses were positive.

Effects of introduction of foods to diet

At the end of the study, sequential expansion of each infant's diet at 2-week intervals was undertaken. A panel of low-allergen foods including potato, pumpkin, zucchini, broccoli, apple, pear, rice, wheat, lamb, and chicken were introduced when these substances had not already been added to the diet. Parents recorded the effect of introduction of these additional foods into the infant's diet with daily diary score cards.

RESULTS

IgE antibodies to foods were elevated in seven infants, and these also showed positive SPT reactions to dietary antigens (Table I). A very high level of skin test reactivity, one that we found diagnostic of immediate clinical hypersensitivity, was demonstrated in response to cow's milk (four cases),¹⁵ egg (six), and peanut (three), although egg and peanut had never been ingested by these patients. Of the seven infants with positive SPT responses to dietary antigens and IgE antibodies to foods, four showed severe eczema.^{11, 16-18}

Within 2 weeks of starting use of Neocate formula, and treatment for eczema as relevant, parents of all patients had reported remission of adverse symptoms. The four patients with growth failure (patients 5, 10, 16, and 18) demonstrated a gradual increase in weight in the several weeks after commencement of use of Neocate formula (see Fig. 2).

Of the 18 infants in the study, two had immediate hypersensitivity reactions, but the remaining 16 completed the 4-week study. Of these 16 patients, 15 satisfactorily completed daily diary symptom score cards, and 14 completed the 24-hour cry/distress charts during the 28-day study period. The parents of one patient (No. 7), who tolerated the active test formula after 7 months of receiving Neocate formula, discarded both daily diary score cards and 24-hour cry/distress charts before final assessment; and the parents of one patient (No. 2) did not complete the 24-hour cry/distress charts

Response to Neocate in M.F.P.I.

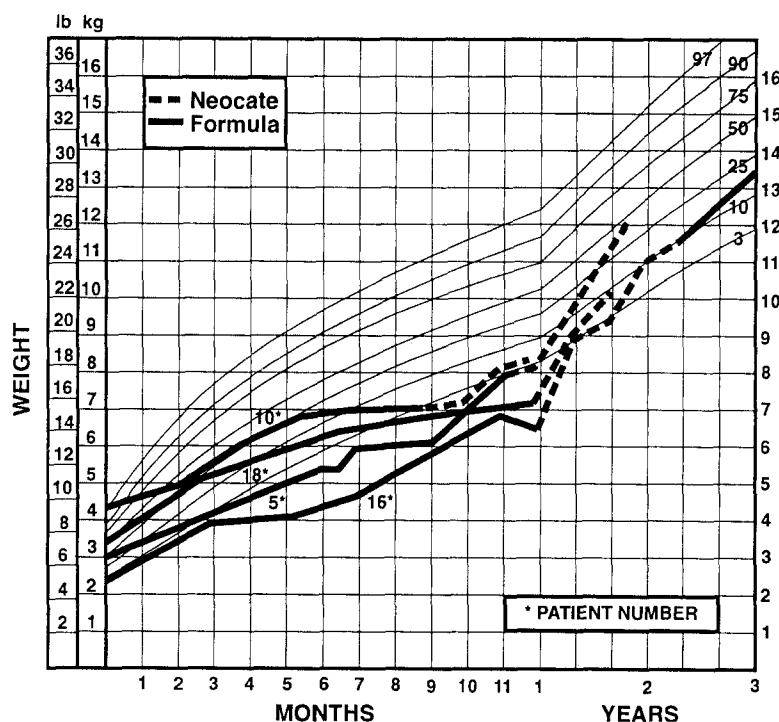


FIG. 2. Change in weight of four infants with growth failure caused by multiple food protein intolerance (M.F.P.I.) before introduction of Neocate formula. Improvement in weight percentiles in the months after commencement of treatment is shown. Patient numbers are indicated.

during the study period. Four patients (Nos. 4, 13, 14, and 15) ceased taking the test formula after 5, 4, 4, and 6 days, respectively, because of the severity of adverse reactions; these patients completed the 4-week study, and when the code was broken, it was found that the active formula had elicited the adverse symptoms.

Outcome of DBPC food challenge

Table II summarizes the effect of formula challenge and other relevant clinical details for each patient.

In six infants (patients 1, 7 to 10, and 16) tolerance to both the active and placebo limbs of the challenge was demonstrated; they were tolerant to Prosobee formula (Mead Johnson, Rydalmere, Australia) (two cases), whey hydrolysate (two), and casein hydrolysate (two). The parents of five of these six infants completed the symptom records. The clinical features and reported range of adverse reactions to both formula and nonformula food for these patients was similar to those of patients who demonstrated intolerance to the test formula. Of the six patients three (patients 1, 7, and 9) showed esophageal inflammation in biopsy specimens before referral, and parents reported

distress behavior that settled with use of Neocate formula. Two patients (Nos. 10 and 16) showed growth failure, which responded to use of Neocate formula (see Fig. 2), and one (patient 8) had severe distress, which settled after Neocate formula was given, tolerated casein hydrolysate in the challenge but had diarrhea, vomiting, and distress within hours of commencing use of cow's milk 8 weeks after the casein hydrolysate-Neocate challenge. As a group, the infants who demonstrated tolerance to the test formula had been ingesting Neocate formula for a median period of 4.5 months (range, 2 to 7 months) before undergoing challenge.

Twelve infants were intolerant to the test formula on DBPC challenge. In two (patients 17 and 18) immediate urticaria and eczema flared within minutes of administration of the active test substance, and the code was broken; Prosobee was the test formula. The parents of the remaining 10 infants reported gradual development of adverse symptoms. Parents of eight of these infants who had distress as a major feature of their adverse response, completed 24-hour distress charts for the entire 4-week study period (patients 3 to 6, and 12 to 15). Although one child (patient 4) who was

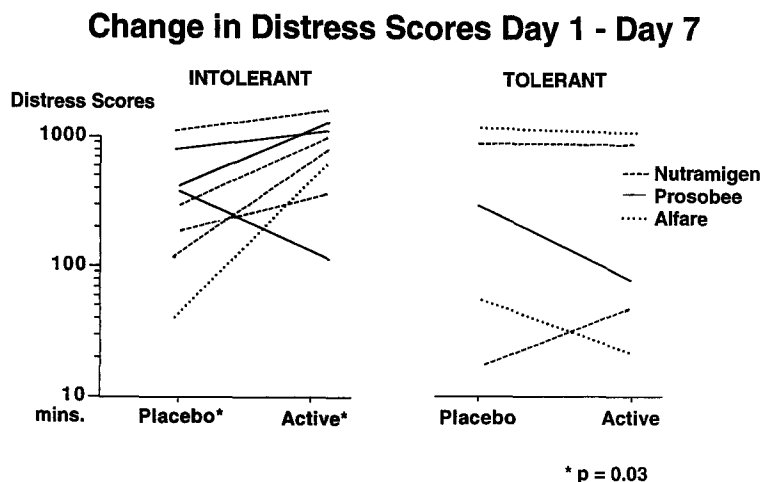


FIG. 3. The sum of distress scores during the days when active formula was used versus the days when control formula was used, according to whether infants were tolerant or intolerant of the challenge. The intolerant infants had significantly increased distress scores while receiving the active formula ($p = 0.03$), whereas those who were tolerant did not. The nature of the test formula used is shown.

TABLE II. Response to formula challenge

Patient No.	Time Neocate taken before challenge (mo)	Challenge formula	Duration of challenge (days)	DBPC challenge symptoms					Outcome
				Irritability	Vomiting	Diarrhea	Eczema	Other*	
1	3	Alfare†	7	—	—	—	—	—	Tolerant
2	3	Alfare	7	+	+	+	—	+	Intolerant
3	2	Prosobee‡	7	+	+	—	—	+	Intolerant
4	12	Prosobee	5	+	+	—	+	—	Intolerant
5	12	Nutramigen‡	7	+	+	+	—	+	Intolerant
6	6	Alfare	7	+	—	+	—	—	Intolerant
7	7	Cow's milk	7	—	—	—	—	—	Tolerant
8	2	Pregestemil†	7	—	—	—	—	—	Tolerant
9	2	Alfare	7	—	—	—	—	—	Tolerant
10	4	Nutramigen	7	—	—	—	—	—	Tolerant
11	3	Prosobee	7	+	—	—	+	—	Intolerant
12	9	Nutramigen	7	+	+	—	—	—	Intolerant
13	3	Nutramigen	4	+	—	+	—	—	Intolerant
14	3½	Prosobee	4	+	—	+	—	—	Intolerant
15	5	Nutramigen	6	+	+	+	+	+	Intolerant
16	4	Prosobee	7	—	—	—	—	—	Tolerant
17	10	Prosobee	1	—	—	—	+	—	Intolerant
18	12	Prosobee	1	—	—	—	+	—	Intolerant

+, Symptom induced by challenge.

*Includes rhinitis and cough.

†Nestle, Australia.

‡Mead Johnson, Australia.

intolerant to soy (on the basis of parental assessment and daily diary scores) showed more distress while receiving the control diet (because of one 24-hour period of unexplained distress), overall the infants with adverse responses to the active test

formula showed significant deterioration of distress ($p = 0.03$), whereas patients tolerant to the active test formula did not (see Fig. 3).

Parents of the 10 infants with slowly evolving adverse reactions completed daily diary symptom

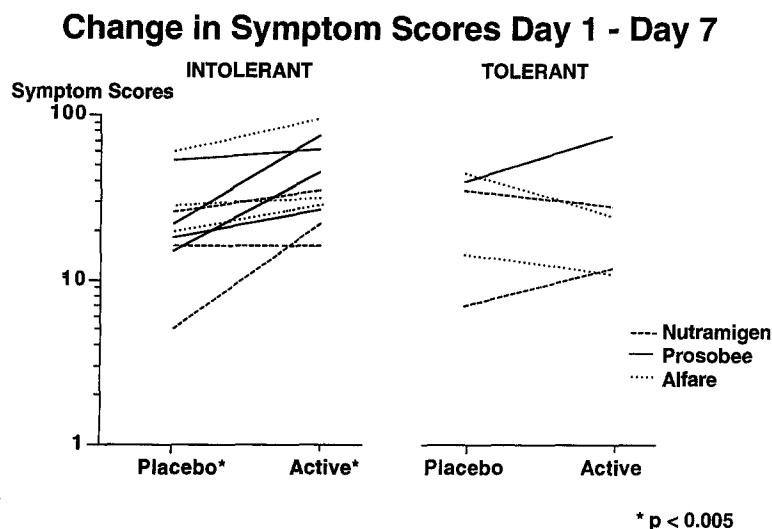


FIG 4. Sum of symptom scores on days active formula was received versus days control formula was received, according to whether infants were tolerant or intolerant to challenge. Symptom scores of intolerant infants increased during the study period ($p < 0.005$), whereas those who were tolerant did not. Test formulas used are shown.

TABLE III. Incidence reported by parents of adverse symptoms of patients at age of 12 months to breast milk, formulas, and panel of 10 low-allergen foods

Food	Tolerant	Intolerant	Reported adverse reaction					Not tried
			Irritability	Vomiting	Diarrhea	Eczema	Other*	
Cow's milk	Nil	17	12	8	3	4	3	1
Soy	Nil	15	8	6	4	4	4	3
Casein hydrolysate	Nil	18	11	5	4	4	4	0
Whey hydrolysate	Nil	13	10	6	6	1	1	5
Breast milk	2	16	9	6	4	3	0	0
Rice	9	7	5	1	3	2	0	2
Wheat	2	6	2	2	1	3	0	10
Potato	8	7	4	2	0	3	0	3
Pumpkin	12	1	0	0	0	1	0	5
Broccoli	9	1	0	1	0	0	0	7
Zucchini	12	0	0	0	0	0	0	6
Apple	9	3	1	1	1	1	0	6
Pear	9	3	1	1	1	1	0	6
Lamb	3	0	0	0	0	0	0	15
Chicken	10	4	2	1	1	2	1	4

*Includes rhinitis and cough.

scores for the 28-day period. A significant increase was observed in symptom scores for the infants who were intolerant to the active test formula ($p < 0.005$) but not for those who were tolerant (Fig. 4). Slowly evolving adverse reactions were noted to Alfare (Nestle, Sydney, Australia) (two patients), Nutramigen (Mead Johnson) (four), and Prosobee (four) within a median period of 7 days (range, 4 to 7) (Table II).

Infants with intolerance to the active test formula, including the two who showed immediate adverse reactions to soy milk, had been ingesting Neocate formula for a median period of 3 months (range, 2 to 12 months) at the time DBPC testing was performed.

There was overall agreement in the parental assessment of the effect of food challenge, identification of the substance causing adverse affect

when relevant, diary records of both infant distress and daily symptom scores, and the physician's assessment of tolerance or intolerance to the test formula. In 11 of the 12 intolerant patients all three criteria for a positive adverse reaction were observed. One patient (No. 4) demonstrated an adverse reaction to the active formula (Prosobee) on the basis of the parental assessment and daily diary scores, but this was not reflected in the 24-hour distress scores.

When adverse reactions to the formula occurred, the symptoms reproduced were those that led to the initial referral of the patients (Tables I and II). Order of the active or control challenge had no effect on the outcome of the procedure.

Adverse reactions to nonformula foods

After stabilization with Neocate formula and the formula challenge procedure, 10 additional low-allergen foods were offered. In some cases parents refused to introduce these additional foods because they had previously attributed adverse reactions to ingestion of them. Table III shows the reported incidence of adverse reactions to various foods introduced after a home challenge procedure. From this panel of 10 foods, adverse reactions were reported to six (range, one to nine) of these foods per patient. Table III also shows the incidence of adverse symptoms associated with breast milk and individual formulas taken before beginning use of Neocate formula. Of interest, in 16 cases parents reported the onset of adverse symptoms while infants were being breast fed only.

DISCUSSION

We have identified a group of infants with chronic ill health attributed to adverse reactions to cow's milk, soy, and extensively hydrolyzed hypoallergenic formulas who responded within 14 days of commencing use of Neocate formula. In two thirds of infants relapse of symptoms occurred after a DBPC challenge with the formula reportedly best tolerated before referral. On the basis of parental reporting, the similar clinical features of the patients, and the spectrum of adverse reactions precipitated by our challenge with the different formulas, we believe that the patients were intolerant to all the formulas they ingested before commencing use of Neocate formula. It is also likely the patients who demonstrated tolerance to the active test formula on DBPC challenge also had the same disease at presentation. The nature of their illness before referral (i.e., documentation of esophageal inflammation, growth failure, severe diarrhea, and

distress symptoms from the first weeks of life), which improved within 14 days of the implementation of the Neocate formula program, and their other clinical features (i.e., the reported incidence of adverse reactions to nonformula foods) are consistent with this disorder. They had been ingesting Neocate formula for nearly 5 months before challenge, suggesting that spontaneous remission of their food protein intolerance, which frequently develops in early childhood,^{6-8, 16} had occurred.

The results of this study confirm an important role for Neocate formula in the treatment of infants and young children with late-onset adverse food reactions to soy and hydrolyzed cow's milk protein formulas. It was well tolerated, and the response in these patients was demonstrated from 72 hours to 14 days after commencement of use. The increase in weight percentiles in the four children with growth failure supports the nutritional adequacy of the preparation. We are not aware of any other studies of large numbers of children with hypersensitivity to multiple hypoallergenic formulas that have examined the value of Neocate formula. However, Kelso and Sampson¹⁷ described one infant with CMA and casein hydrolysate hypersensitivity after DBPC challenge who tolerated Neocate formula. Iacono et al.¹⁸ described one infant with multiple food hypersensitivity to cow's milk, soy milk, and extensively hydrolyzed formula who required total parenteral nutrition from the age of 4 months. After more than 30 days of total parenteral nutrition, her condition stabilized with a dietary supplement exclusively based on carbohydrate, lipids, and a mixture of simple amino acids. Of interest, the patient was intolerant of rice, beef, chicken, wheat, lamb, and multiple infant formulas: a spectrum of adverse reactions to formula and other foods described by parents of many of our patients.

Several investigators have described immediate hypersensitivity reactions to casein hydrolysate,¹⁹ whey hydrolysate,²⁰ and soy formula.²¹ This study confirms our earlier observations^{1, 2, 6} that these formulas also elicit slowly evolving symptoms (i.e., late-onset reactions occurring several days after commencement of modest amounts of formula [approximately 300 ml/day]). Although the entire 4-week study could not be conducted in an inpatient hospital setting, the consistency of parental observations among patients and the similar effect of the active test formula when compared with the presenting symptoms support the validity of the test procedure and the outcome of the challenges.

These late-onset reactions should be contrasted

with the findings of Sampson and Bock, who identified only immediate-type hypersensitivity responses to foods on challenge.²² However, Sampson's patients were atopic children (median age, 4.7 years) who had eczema,²³ whereas our patients had predominantly gastrointestinal symptoms (although in some cases such symptoms were associated with slowly evolving eczema) and had a median age of 7 months. Furthermore, Bock²⁴ has described adverse reactions to foods in non-IgE-sensitized infants in community-based studies. The results of our study confirm the existence of late-onset adverse reactions to foods with DBPC challenge methods. It should be noted that the food challenge procedure used in this study, which starts at a low dose (to avoid as much as possible the severe adverse reactions of the type seen in two of our patients), extends the time between the commencement of food challenge and the onset of symptoms. In addition, the method of gradually increasing the dose of antigen until full amounts are reached on day 3 may induce partial desensitization, further modifying and downregulating the rate of reaction.²³ On the other hand, the slow evolution of reactions, where the relationship between the commencement of the food and onset of adverse symptoms is difficult to define, is consistent with the parental observation of the effects of these foods in the actual situation.

This and previous studies from our clinic suggest that intolerance to soy and extensively hydrolyzed infant formulas is not an uncommon problem in infants with food hypersensitivity who attend a specialist center.^{1, 2, 6} Because most of the adverse reactions occur when protein-containing foods such as hydrolyzed formula, soy, milk, egg, wheat, peanut, fish, meats, and rice are ingested, we have called this syndrome multiple food protein intolerance of infancy. The development of a nutritionally complete amino acid-based formula for infant use appears to be a significant advance in the treatment of infants with multiple food protein intolerance and those with other food protein hypersensitivities.

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