

The natural history of intolerance to soy and extensively hydrolyzed formula in infants with multiple food protein intolerance

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Infants (n = 18) with intolerance to extensively hydrolyzed formulas and soy who responded to an L-amino acid–based elemental formula (AAF) were studied until 3 years of age. By 2 years of age most tolerated non-formula foods, and by 3 years only 3 required AAF. Growth normalized during AAF feeding in 4 infants with failure to thrive. (J Pediatr 1999;135:118-21)

We have previously described a group of infants who were intolerant to soy, extensively hydrolyzed formulas, and a wide range of other food proteins. We called this disorder *multiple food protein intolerance of infancy*.¹ Vanderhoof et al² and de Boissieu et al³ have reported on their experience with infants intolerant to extensively hydrolyzed casein and whey preparations. Both studies noted patients intolerant to other foods and formula, although these were not described in detail. In all reports symptoms remitted within 2 weeks of commencement of feeding with an elemental amino acid–based complete infant formula (Neocate, SHS Liverpool). Recently, Bines et al⁴ have reported a group of children with short bowel syndrome and intolerance to extensively hydrolyzed formula who ex-

perienced a significant improvement in absorptive function after commencement of AAF feeding, enabling them to cease total parenteral nutrition.

Infants with MFPI need to be distinguished from those with hypersensitivity to several common food proteins such as cow's milk, egg, and peanut who tolerate soy or extensively hydrolyzed formula. We have described these patients as having "oligo" food protein hypersensitivity.⁵ Although patients with oligo food allergy do have hypersensitivity to multiple food proteins, they usually tolerate extensively hydrolyzed formula and do not encounter the complex nutritional problems or have the range of food intolerances of patients with MFPI.

This report summarizes the outcome of our initial cohort of 18 infants with

MFPI intolerant to soy and extensively hydrolyzed formula, until the age of 3 years.

AAF	Amino acid–based formula
AD	Atopic dermatitis
DBPC	Double-blind, placebo-controlled
EHCF	Extensively hydrolyzed casein formula
EHWH	Extensively hydrolyzed whey formula
MFPI	Multiple food protein intolerance of infancy
SPT	Skin prick test

PATIENTS AND METHODS

Detailed clinical features of the 18 infants in this cohort have been previously described.¹ In summary, there were 11 boys and 7 girls (mean age at presentation, 7.3 ± 0.76 months; SE) who presented with irritability (n = 13), vomiting (n = 13), diarrhea (n = 5), atopic dermatitis (n = 6), and growth failure (n = 4). In 16, symptoms developed while they were receiving only breast milk and persisted during ingestion of extensively hydrolyzed casein formula (n = 18), soy (n = 15), and extensively hydrolyzed whey formula (n = 13). In all 18 infants, symptoms remitted within 14 days of the commencement of AAF feeding. After remission of symptoms had been achieved for 2 weeks, a small number of foods including rice, potato, pumpkin, and zucchini were sequentially added at 2- to 4-week intervals.

Double-blind, placebo-controlled challenges were performed 4 months

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Table. Development of food tolerance in 18 infants with MFPI

Foods	<12 months			12-24 months			24-36 months		
	Intolerant	Tolerant	Not tried	Intolerant	Tolerant	Not tried	Intolerant	Tolerant	Not tried
Formulas									
Casein hydrolysate	16	2	0	2	4*	10	0	1	11
Whey hydrolysate	11	2	5	0	0	16	0	1	15
Cow's milk	16	1	1	5	3*	9	5	4*	5
Soy	14	1	3	6	1	10	1	2	13
Grains									
Rice	7	9	2	2	7	0	1	1	0
Wheat	6	2	10	2	9	5	0	3	4
Egg	7	0	11	2	1	15	4	2	11
Peanut	5	0	13	1	1	16	4	2	11
Meat									
Chicken	5	6	7	0	9	3	1	1	1
Beef	0	3	15	0	6	9	0	4	5
Lamb	1	5	12	1	7	5	0	1	5
Fish	0	1	17	1	4	12	1	2	10
Fruit and vegetables									
Potato	6	9	3	2	5	2	0	2	2
Pumpkin	2	12	4	2	4	0	1	1	0
Broccoli	0	11	7	2	4	1	1	1	1
Zucchini	0	12	6	0	4	2	0	0	2
Apple	3	9	6	1	6	2	0	1	2
Pear	3	9	6	2	5	2	0	2	2
Banana	1	7	10	1	4	6	2	1	4

Patients in whom tolerance to a food item has developed are not included in the total of the subsequent age group.

*Three of the patients who tolerated extensively hydrolyzed casein subsequently tolerated cow's milk formula.

(range, 2 to 12 months) after commencement of AAF feeding. After these DBPC challenges had been completed, additional low-allergen foods such as apple, pear, chicken, lamb, and wheat (including those above if not previously tolerated) were introduced at 2-week intervals. These foods were re-introduced 2 months later if not tolerated initially, and if adverse symptoms recurred, subsequent re-challenge was deferred for 6 months. Formulas were re-challenged, depending on parental consent at 6- to 12-month intervals. Cow's milk, egg, and peanut were introduced once low-allergen formulas had been tolerated.

Standard skin prick tests with common food allergens (including cow's milk, egg, and peanut) were performed in all patients at initial presentation.⁶ If

SPT results were highly positive (4+; >6 mm, ie, levels that we have shown to be diagnostic of IgE food allergy^{7,8}), patients were not challenged with this allergen, and SPTs were repeated about 12 months later.

Growth parameters were documented every 2 to 3 months. Z scores⁹ for weight-for-age and height-for-age were calculated by using an anthropometric software program (Centers for Disease Control and Prevention, Atlanta, Ga).

RESULTS

In the initial study all 18 patients were ingesting EHCF and were clinically intolerant. These patients had a history of intolerance to cow's milk for-

mula (n = 17), soy formula (n = 15), and EHWF (n = 13). Adverse symptoms resolved within 2 weeks of commencement of AAF feeding.¹ After a median period of 3.6 months (range, 2 to 7 months), DBPC challenges in 6 infants demonstrated tolerance to soy milk (n = 1), cow's milk (n = 1), EHCF (n = 2), and EHWF (n = 2). The remaining 12 infants were intolerant to EHCF (n = 4), EHWF (n = 2), and soy (n = 6). These results have been reported in detail elsewhere.¹

The 12 patients who were intolerant to the challenge formula were re-challenged in the second and third years of life. Five of 8 patients challenged with cow's milk, 6 of 7 challenged with soy, and 2 of 6 challenged with EHCF were intolerant. Three patients who tolerated EHCF formula subsequently toler-

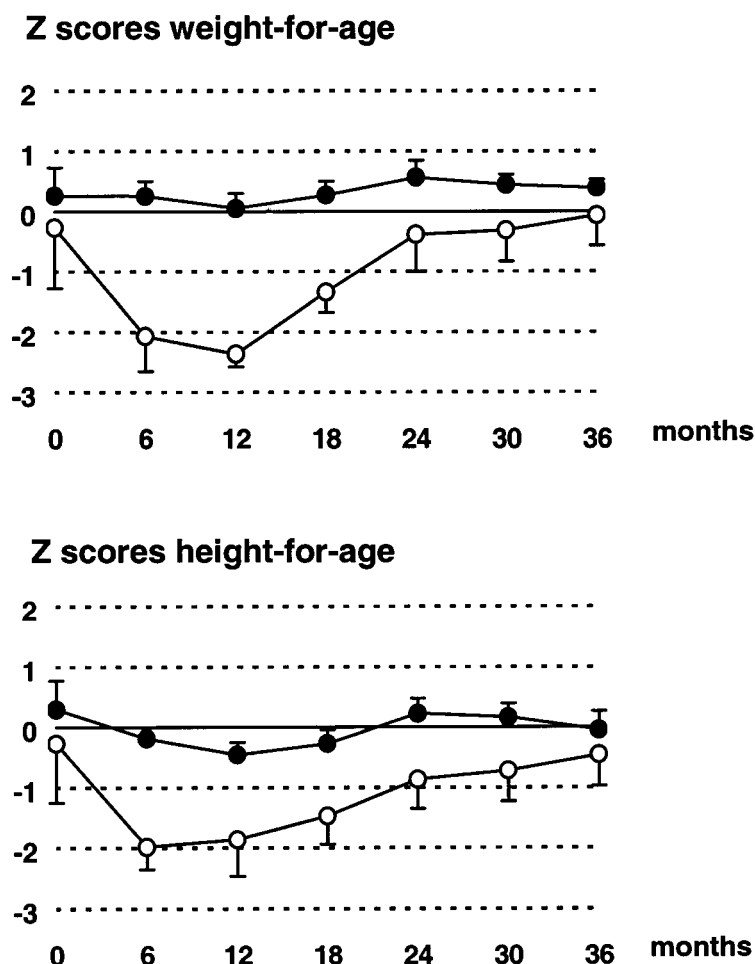


Figure. Mean Z scores (SE bars) in 18 infants with MFPI from 0 to 36 months of age. **A**, Weight-for-age. **B**, Height-for-age. Fourteen infants had normal weight gain (●), and 4 infants presented with failure to thrive (○).

ated cow's milk formula. Most patients tolerated cereal, meats, fruits, and vegetables by the end of the second year. Further remissions were seen in the third year (Table). By 36 months of age, only 3 patients required AAF for ongoing nutritional support.

In the initial study, 7 of 18 infants had highly positive SPT responses to cow's milk, egg, or peanut; 5 of them presented with atopic dermatitis (AD+) and 2 did not (AD-). Persistence of IgE hypersensitivity to cow's milk, egg, or peanut beyond the age of 3 years was seen more frequently in infants with AD (Fisher exact test: cow's milk 5/5 AD+ vs 1/8 AD-, $P = .002$; egg 5/5 AD+ vs 1/4 AD-, $P = .02$; peanut 4/4 AD+ vs 0/5 AD-, $P = .003$).

The 4 patients who presented with

significant failure to thrive (mean Z score for age-for-weight of -2.4) had achieved catch-up growth within 6 to 12 weeks of commencement of AAF feeding. At about 24 months of age, their poor weight gain had reversed to a mean Z score of -0.4 . This was maintained at 36 months of age. Linear growth was similarly affected. At 6 months, the mean Z score for height-for-age was -2.0 . There was a gradual increase toward a mean Z score of -0.4 at 36 months of age (Figure).

DISCUSSION

All infants with MFPI and intolerance to EHCF, EHWF, and soy formula responded to treatment with AAF.

Most tolerated low-allergen foods such as grains, vegetables, fruits, and meats in the second year of life. Vanderhoof et al² reported transient intolerance to EHCF, which remitted within 2 weeks of commencing AAF feeding in 8 of 25 patients. We found that 2 of 6 children who were initially intolerant to EHCF became tolerant to it within 3 months of commencing AAF feeding. Subsequently, another 4 of 6 became tolerant in the second year of life. Although soy intolerance is reportedly uncommon in children with food allergy,¹⁰ it was demonstrated in 6 of 7 of our patients until the age of 2 years. A minority of patients required long-term nutritional support with AAF, particularly if they had features of IgE sensitization. This finding is in agreement with our previous long-term follow-up study of food allergy in which infants with atopic features had a significantly higher incidence of persistent IgE food allergy to cow's milk, egg, and peanut.¹¹

Isolauri et al,¹² in a study of infants with cow's milk allergy, described normal growth in infants receiving AAF. Our study has demonstrated that infants presenting with failure to thrive caused by food protein hypersensitivity were able to achieve normal growth during AAF feeding in the second year of life. Improved growth rates are a consequence of improved delivery of protein and energy and control of nutrient loss from vomiting and diarrhea. In addition, Neocate has a slightly higher protein content than extensively hydrolyzed formula, which may have advantages in infants with protein-energy malnutrition.¹² The finding of high plasma concentrations of essential amino acids in infants receiving AAF compared with breast-fed infants¹² is of uncertain significance and underlines the need for long-term follow-up of patients receiving AAF.

There are several limitations to this study. First, we have included in the present report 6 patients whose symptoms initially remitted while receiving AAF and who tolerated low-allergen

formula on subsequent challenge. These infants have been included in this report on the strength of the severity of their initial symptoms, the complexity of their intolerances, and their response to AAF. Although we cannot prove that these infants have been truly intolerant of extensively hydrolyzed formula, we believe that it is likely that spontaneous remission of formula intolerance has occurred before challenge. Second, it was not possible to perform all formula and food challenges in a DBPC manner. Challenges may take up to several weeks, and parents were often reluctant to undertake prolonged formal challenges after stabilization of their infant's health had been achieved.

Despite these limitations and the retrospective nature of this report, we have found further evidence that AAF offers a valuable treatment for infants with MFPI who are intolerant to soy and extensively hydrolyzed formulas. Intolerances are usually transient in nature but may persist beyond 2 years of age, particularly if associated with features of IgE sensitization.

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