

CLINICAL AND LABORATORY OBSERVATIONS

Allergy to extensively hydrolyzed cow's milk proteins in infants: Safety and duration of amino acid-based formula

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Infants (n = 52) allergic to cow's milk protein and extensively hydrolyzed formulas received an amino acid-based formula. The amino acid-based formula proved to be safe, with infants exhibiting an overall gain in length and weight. Children with allergy restricted to extensively hydrolyzed formulas were diagnosed earlier and tolerated cow's milk protein earlier than children with multiple food allergy. (J Pediatr 2002;141:271-3)

Treatment of cow's milk protein (CMP) hypersensitivity is based exclusively on diet, generally using an extensively hydrolyzed formula (EHF). Approximately 90% of children allergic to CMP respond^{1,2}; thus other options are needed for those allergic to EHF.³ The availability of an amino acid-based formula (AABF) (Neocate, SHS International Ltd, Liverpool, United Kingdom),^{4,5} provided one option and offered the ability to refine the diagnosis of EHF allergy.⁶⁻⁹ Allergy to EHF may be part of a more severe syndrome, multiple food allergy, as defined by Hill et al.⁹ The time course may differ according to the presence or absence of associated food allergy.¹⁰ We carried out a survey, extending up

to 69 months, in follow-up of patients with EHF allergy; this allowed us to assess the safety of long-term use of an AABF and to analyze the potential duration of its use according to the clinical presentation.

METHODS

These 52 infants (26 boys) with EHF allergy, 5.3 ± 3.8 months of age, include the two cohorts previously depicted.^{6,10} All those with adverse reactions to CMP were referred because of persisting clinical symptoms despite CMP elimination, with soy and EHF as replacement diets. Nine had never received CMP since birth because of food

allergy in first-degree relatives and were fed breast milk (n = 4) or received an EHF (n = 5). When allergy to EHF was diagnosed, diversification of the diet was delayed, vegetables and fruits being introduced after 6 months of age, meat one month later, and eggs, fish, and tropical fruits after 1 year of age. Nuts and peanuts were always excluded until the child was older than 3 years. The

AABF	Amino acid-based formula
CMP	Cow's milk protein
EHF	Extensively hydrolyzed formula

AABF was instituted, children were orally challenged after one month with the EHF previously used.¹⁰ In the case of a positive test, infants were rechallenged with an EHF before the 1 year of age, then every 6 months until 2 years of age. When the challenge indicated tolerance of EHF or in children above age 2 years, the challenge was performed with CMP, according to the same protocol, once per year.

When allergy to non-CMP food was suspected in an infant, skin prick tests were performed and an elimination diet, followed by a single blind-oral challenge, was done for each suspected food.

Height and weight Z scores were calculated at time of diagnosis and at the end of the survey. Statistical analysis was performed with the use of the Stat-View program (ABACUS Concepts, Inc, Berkeley, Calif). For statistical evalua-

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Table I. Clinical data of patients with EHF allergy: Tolerance of CMP before or after 20.5 months (median age of tolerance)

	Age at CMP tolerance (mo)		P value
	<20.5 (n = 26)	>20.5 (n = 26)	
Age at onset of symptoms (mo)	1.9 ± 1.2	2.0 ± 2.3	NS
Age at diagnosis (mo)	3.4 ± 2.2	7.0 ± 4.3	.03
Age at introduction of solid food (mo)	6.2 ± 0.9	5.1 ± 2.4	.05
Duration of AABF (mo)	8.2 ± 3.6	17.2 ± 9.9	< .0001
Clinical symptoms			
Digestive (n)	25	22	NS
Eczema (n)	5	18	.002
Failure to thrive (n)	7	9	NS
Malaise (n)	8	0	.001
Angioedema (n)	0	6	.008
Evolution of food allergy			
Isolated EHF allergy (n)	17	1	< .001
Oligofood allergy (n)	8	13	ns
Multiple food allergy (n)	1	12	.002

NS, Not significant.

Table II. Clinical data and outcome of patients in relation to an association with other food allergy

	Isolated EHF allergy (a)	Oligofood allergy (b)	Multiple food allergy (c)	P value a vs b/b vs c/a vs c
Patients (n)	18	21	13	
Age at onset of symptoms	1.7 ± 0.7	1.9 ± 1.2	2.4 ± 2.0	NS/NS/NS
Age at diagnosis	3.4 ± 1.8	5.4 ± 3.4	7.6 ± 5.1	.05/NS/.002
Age at EHF tolerance	10.5 ± 3.1	13.4 ± 6.2	20.0 ± 5.3	NS/.04/.004
Age at CMP tolerance ^o	13.4 ± 3.9	21.7 ± 8.3	34.5 ± 11.7	.003/.004/<.001
Duration of AABF	7.1 ± 2.2	13.5 ± 7.4	20.0 ± 11.8	.008/.02/<.001
Age at introduction of solid food	6.4 ± 1.2	5.1 ± 1.5	5.4 ± 2.7	.002/NS/NS
Symptoms				
Digestive (n)	17	20	10	NS/NS/NS
Eczema (n)	4	11	8	NS/NS/.03
Failure to thrive (n)	8	2	5	NS/NS/NS
Malaise (n)	5	3	0	NS/NS/.04
Angioedema (n)	0	4	2	NS/NS/NS

NS, Not significant.

Age is expressed in months.

^oThe 11 children still intolerant to CMP at the end of the survey were included in statistical analysis with an age of CMP tolerance assumed to be equal to their age at the end of survey.

tions, analysis of variance and the χ^2 test were used.

RESULTS

Twenty-one patients had allergy to fewer than 6 foods, so-called "oligo-food" allergic, and 13 patients had multiple food allergy as defined by Hill.¹¹ The AABF was used for a

mean duration of 11.4 ± 7.9 months (range, 3.5-41) and proved to be safe in all cases: the Z score increased in the entire cohort from -0.86 ± 1.37 to 0.16 ± 1.38 for height ($P < .001$) and from -1.04 ± 1.45 to -0.02 ± 1.16 for weight ($P < .001$). CMP tolerance occurred at <1 year of age in 8 children, 1 to 2 years in 22, 2 to 3 years in 8, and >3 years in 14. Eleven children did not tolerate CMP by the end of

the survey period, the oldest being 5.5 years old. The median age of CMP tolerance was 20.5 months (Table I).

Table II provides an analysis according to the absence or presence of allergy to other foods, oligofood, or multiple food allergy. Children with isolated EHF allergy tolerated CMP earlier than those with multiple food allergy and were also diagnosed earlier.

DISCUSSION

This study depicts the clinical evolution of infants allergic to both CMP and EHF and demonstrates the safety of an AABF. The course of EHF allergy differs according to the association with allergy to other foods.¹⁰ In the presence of allergy to other foods, tolerance of EHF and of CMP occurs later and a restricted diet based on AABF is required for a longer duration. Our observations fit with the recent description of the use of an AABF¹² in 31 consecutive children, of whom 29 had multiple food allergy and 13 had not tolerated EHF.

The different course according to associated food allergies implies potential differences in the timing of onset or diagnosis of the disease. In our previous analysis, patients with isolated EHF allergy had exclusively digestive symptoms and were also diagnosed earlier.¹⁰ In the current series, even though symptoms began at the same age, an earlier diagnosis was a factor indicating a good prognosis, implying both a shorter duration of symptoms and a decreased number of foods involved. Digestive symptoms still dominate in children with isolated EHF allergy. In the description by Hill et al⁹ of children with multiple food allergy

and dominant digestive symptoms, 6 of 17 had atopic dermatitis, and the mean age at diagnosis was 7.3 ± 0.3 months. Early recognition might explain why in the current series, a prompt diagnosis led to a delayed introduction of solid foods, which might, in turn, participate in the improvement of the tolerance process.

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