

Hypersensitivity to hydrolyzed cow's milk protein formula in infants and young children with atopic eczema/dermatitis syndrome with cow's milk protein allergy

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Abstract

Purpose: Atopic eczema/dermatitis syndrome (AEDS) is often the first manifestation of atopic disease in children. Food hypersensitivity should be considered in approximately 40% of these patients. AEDS children with cow's milk allergy are commonly prescribed a hydrolyzed formula or amino acid-based formulas for an alternative protein source. The aim of this study was to investigate hypersensitivity to extensive hydrolyzed casein and whey proteins in AEDS children with cow's milk protein allergy (CMA).

Material and methods: The study included 67 hospitalized children with AEDS (m/f – 43/24), aged 1-28 months (mean 11.34 ± 8.52) and CMA confirmed by oral food challenge. All patients were treated with extensively hydrolyzed formulas: 48/67 children with casein hydrolysates and 19/67 children with whey hydrolysates.

Results: In most of studied children we recognized severe AEDS (SCORAD Index: mean 55.41 ± 17.4 ; 95% CI 51.17-59.66) with elevated total IgE (mean 432.98 ± 1030.46 ; 95% CI 181.63-684.33). In 22/67 children (32.8%) we established diagnosis of hypersensitivities to hydrolyzed formula (HHF): in 17/22 to casein hydrolysates, in 4/22 to whey hydrolysates and in 1/22 to amino-acid based formula. Children with HHF did not differ in the severity of AEDS evaluated by SCORAD (57.18 ± 16.59 vs 54.56 ± 17.90), the serum level of total IgE (603.9 ± 1253 vs 349.4 ± 906.1) and the time of breast-feeding (4.4 ± 4.0 months vs 6.8 ± 7.28). They differ in the number of plasma eosinophils and positive correlation between number of eosinophils and serum level of total IgE ($p < 0.05$, $r = 0.46$ vs $r = 0.07$).

Conclusions: Children with moderate or severe atopic eczema/dermatitis syndrome can demonstrate hypersensitivity to hydrolyzed formula recommended for therapeutic indications.

Key words: atopic eczema/dermatitis syndrome, extensively hydrolyzed formula, cow's milk protein, amino acid-based formula.

Abbreviations: AAF – amino acid-based formula; AEDS – atopic eczema/dermatitis syndrome; CI – confidence interval; CM – cow's milk; CMA – cow's milk allergy; DBPCFC – double-blind, placebo-controlled, food challenge; eHC – extensive hydrolysates of casein; eHW – extensive hydrolysates of whey.

Introduction

Atopic eczema/dermatitis syndrome (AEDS) is a common ailment in children, affecting 10% to 12% of infants [1]. It is often regarded as the first manifestation of atopic disease in children. Patients with AEDS have in general an elevated total and food-specific level of IgE antibodies and food hypersensitivity should be considered in approximately 40% of these children [1,2]. Sensitivity to foods is seen in the first few years of life, while older children and adults with AEDS are more predisposed to developing respiratory allergy. The most commonly offending foods are cow's milk (CM), hen's egg, wheat and soy [3]. Cow's milk allergy affects 2% to 3% of infants in unselected cohorts [4]. Approximately one-third of the children with AEDS have been diagnosed with cow's milk allergy or cow's milk intolerance, as determined by means of an elimination diet and challenges, and approximately 40% to 50% of children <1 year of age with cow's milk allergy or cow's milk intolerance have AEDS [5]. Hill et al. found AEDS in 57% of the children with IgE-mediated cow's milk allergy [6].

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Table 1. Characteristics of AEDS children with or without hypersensitivity to hydrolyzed formulas

	Children with hypersensitivity to hydrolysates formulas (n=22)	Children without hypersensitivity to hydrolysates formulas (n=45)	p value
Sex (f/m)	8/14	16/29	
Age, mo (mean \pm SD) (median) (95% CI)	11.95 \pm 8.3 (9.5) (8.3-15.6)	11.04 \pm 8.8 (7.0) (8.4-13.7)	<0.69=ns
SCORAD (mean \pm SD) (median) (95% CI)	57.18 \pm 16.6 (58.5) (49.8-64.5)	54.56 \pm 17.9 (52.0) (49.2-59.9)	<0.57=ns
IgE IU/ml (mean \pm SD) (median) (95% CI)	603.9 \pm 1253.5 (75.5) (48.14-1159.7)	349.4 \pm 906.1 (34) (77.2-621.7)	<0.35=ns
Number of peripheral eosinophils (mean \pm SD) (median) (95% CI)	10.3 \pm 8.2 (8.0) (6.7-13.9)	5.7 \pm 4.0 (4.0) (4.5-6.9)	<0.02
Time of breast-feeding in months (mean \pm SD) (median) (95% CI)	4.4 \pm 4.0 (4.0) (2.9-5.9)	6.8 \pm 7.28 (4.5) (4.6-9.0)	<0.29=ns

An avoidance diet plays an important role in the treatment of AEDS particularly in small children. Formulas containing hydrolyzed cow's milk proteins are used to treat these infants. Partially or extensively hydrolyzed formulas or amino acid-based formulas can be used depending on the severity of the clinical course of AEDS. The incidence of adverse reactions or allergy to these formulas in infants has been a new clinical problem in recent years.

The aim of this study was to investigate hypersensitivity to extensive hydrolysates of casein and to extensive hydrolysates of whey protein in children up to 3 years of age with AEDS.

Material and methods

The study included 67 hospitalized children with AEDS (43 boys, 24 girls), aged 1-28 months (mean 11.34 \pm 8.52; 95% CI 9.24-13.44). The inclusion criteria were: 1. diagnosis of AEDS, 2. age up to 3 years, 3. case history of CMA. The exclusion criteria: 1. concomitance of other organ diseases, 2. lack of parents consent to the study.

We used the diagnostic criteria of atopic dermatitis by Hanifin and Rajka [7] and SCORAD Index adapted by European Task Force on Atopic Dermatitis [8]. Scoring of AEDS included: assessment of topography items (affected skin area), intensity criteria (extent of erythema, edema, crusts, excoriations, lichenification and xerosis), and subjective parameters (extent of itch and loss of sleep). The maximum score was 92 points.

Cow's milk allergy (CMA) was recognized: 1) on the basis of case and family history, 2) by prick skin tests with native food allergens, 3) laboratory data: total IgE, food-specific IgE (cow's milk proteins: casein and whey protein: α -lactoalbumin and β -lactoglobulin) and 4) oral open CM challenge. The total IgE concentration and serum-specific IgE antibodies to CM allergens were measured with a fluoroenzymatic assay

(UniCAP Pharmacia & Upjohn Diagnostics, Uppsala, Sweden) as detailed by the manufacturer's details and the cut-off point for positivity was set at 0.7 kU/l. Open challenge was chosen, since it has been shown to be reliable method in young children. Children taking antihistamine were advised to avoid it for 72 hours before provocation. The challenge was started in the hospital and then continued in the patient's home where the parents recorded the symptoms. The challenge period was 2 weeks. During the first day successive and increasing doses (0.1, 1.0, 3.0, 10.0, 30.0 and 50 or 100 ml – according to age of life) low-lactose CM (Bebilon Nutricia) were administered. Challenge was performed with the access to full emergency equipment with antianaphylactic drugs. After CMA diagnosis, all patients were treated with cow's milk protein hydrolyzed formula: 48/67 (71.6%) children with extensive hydrolysates of casein (eHC) (Nutramigen; Mead Johnson) and 19/67 (28.4%) children with extensive hydrolysates of whey (eHW) (Bebilon pepti 1 or 2; Nutricia). Introduction of hydrolyzed formula and monitoring of its clinical tolerance was started during hospitalization and continued in the out-patient department. Intolerance symptoms were indication to changing formula (eHC or eHW or AAF).

Statistical analyses

SCORAD, IgE, plasma eosinophils and the time of breast feeding data are expressed as mean (95% CI) and median values. The Mann-Whitney nonparametric test was used to compare the results of patients with those of controls. Results were considered statistically significant at $p < 0.05$.

Ethics

Informed consent was obtained from the parents. The study was approved by the Ethics Committee of Medical University of Bialystok.

Results

Tab. 1 shows the characteristics of the patients examined. In most of studied patients we recognized severe AEDS: SCORAD Index: range 18-92, mean 55.41 \pm 17.4 (95% CI 51.17-59.66) (Fig. 1) with elevated total IgE: range 2-5000IU, mean 432.98 \pm 1030.46 (95% CI 181.63-684.33). In 22 of 67 AEDS children (32.8%) we established diagnosis of hypersensitivities to hydrolyzed formulas (HHF): in 17/22 to extensive hydrolysates of casein (17 of 48 treated with eHC), in 4/22 to extensive hydrolysates of whey protein (4 of 19 treated with eHW) (Fig. 2). One of 22 children had reaction to amino acid-based formula. Children with hypersensitivity to hydrolyzed formulas did not differ in the intensity of AEDS evaluated by SCORAD (57.18 \pm 16.59 vs. 54.56 \pm 17.90) (Tab. 1). In HHF group the serum level of total IgE was higher than in children without HHF, but the difference was not significant (Fig. 3). In these both studied groups, we did not find the significant correlation between the serum IgE and SCORAD (Fig. 4, Fig. 5). Exclusively in children with HHF we noted a significant higher number of eosinophilic granulocytes in peripheral blood ($p < 0.02$) (Tab. 1) and high positive correlation between number of eosinophils and serum level of total IgE ($p < 0.05$, $r = 0.46$ vs. $r = 0.07$) (Fig. 6, 7).

Figure 1. SCORAD index in studied AEDS children

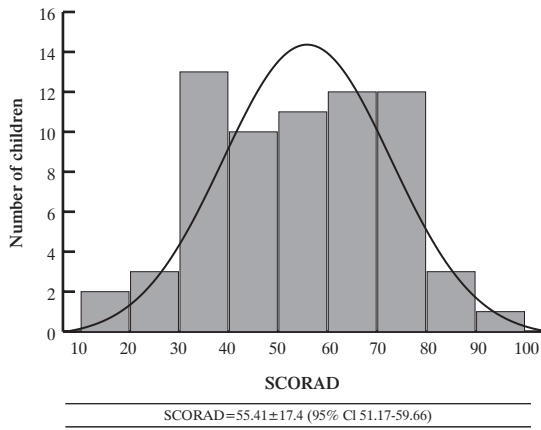


Figure 2. Hypersensitivity to hydrolysates in AEDS children

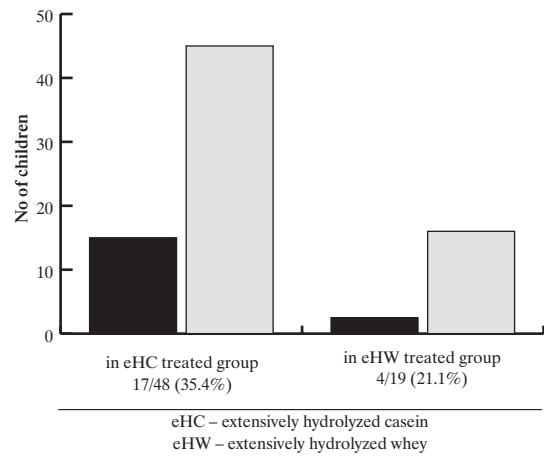


Figure 3. Total serum IgE in AEDS children with or without hypersensitivity to hydrolyzed formula

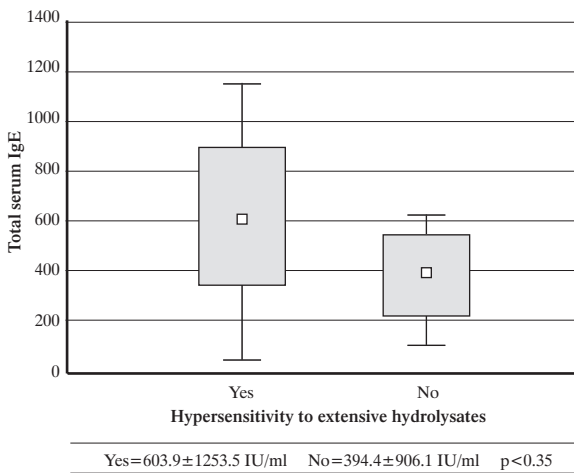


Figure 4. IgE vs SCORAD in children with hypersensitivity to hydrolysates (r=0.27)

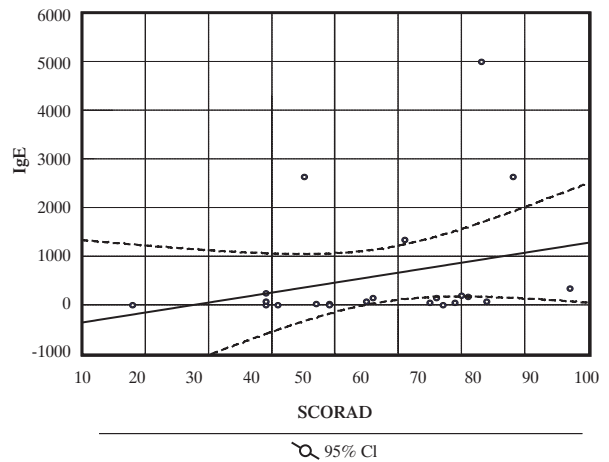
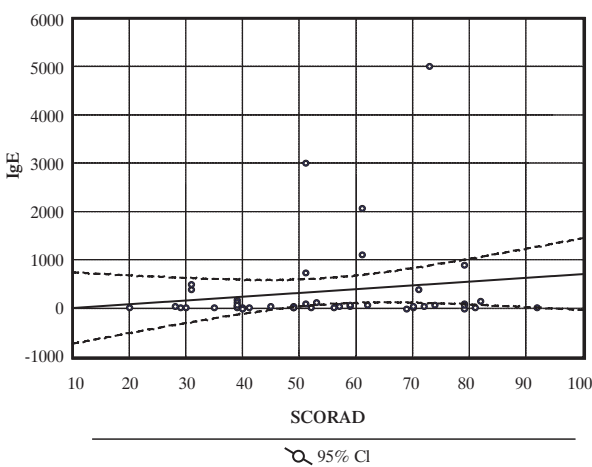


Figure 5. IgE vs SCORAD in children without hypersensitivity to hydrolysates (r=0.15)



Clinical symptoms of hypersensitivity (dermatological, gastrointestinal and from nervous system) were observed in 17 of 48 (35.4%) AEDS patients treated with eHC and in 4 of 19 (21.1%)

treated with eHW, 4 children did not tolerate as well eHC as eHW and were successfully treated with AAF (Tab. 2).

In studied group of 67 children mean time of breast feeding was 5.84 ± 6.01 months (95% CI 4.13-7.55). The shortest time of breast feeding we noted in 4 infants with hypersensitivity to both hydrolysates (3.6 ± 2.7) but the difference between patients with and without HHF was insignificant (Tab. 1, Fig. 8).

Discussion

Food allergy plays a role in at least 20% of the cases of AEDS in children younger than 4 years and in about 30% of AEDS children CMA is recognized [5]. All of AEDS children included to our study presented clinical symptoms of CMA confirmed by open oral cow's milk challenge. The complete elimination of cow's milk protein from the child diet for a variable period time is vital to the management of cow's milk allergy and extensively hydrolyzed formulas are the first-line therapy for routine use [9,10]. In this study most of patients (71.6%) were treated with eHC in the beginning. Protein hydrolysates are used to the

Figure 6. Plasma eosinophils vs serum IgE in AEDS children with HHF (r=0.46)

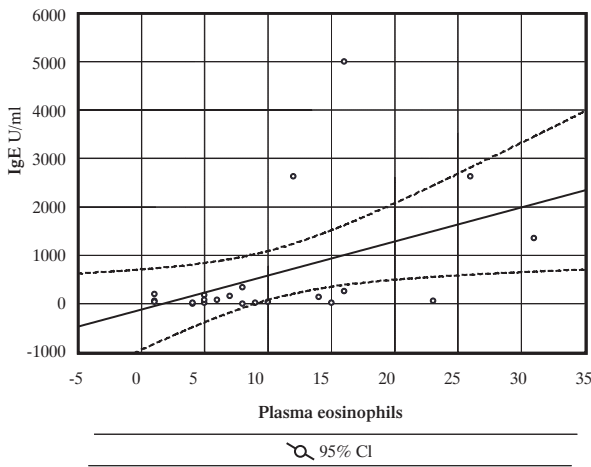


Figure 7. Plasma eosinophils vs serum IgE in AEDS children without HHF (r=0.07)

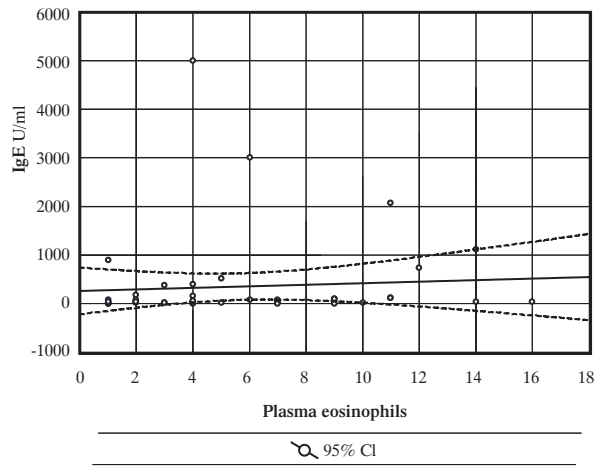


Table 2. Characteristics of AEDS children with cow's milk allergy and hypersensitivity to hydrolyzed formula

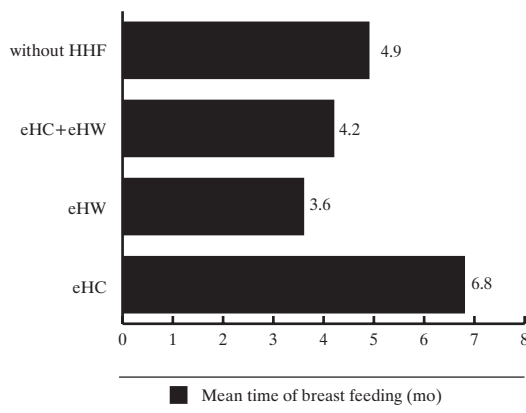
Patient	Age (mo)	Sex (F/M)	No tolerated extensively hydrolyzed protein	Clinical symptoms of hypersensitivity					Total IgE (UI/ml)	IgE caseine (class)	IgE whey (class)	
				Dermato-logical Exacer- abtion of AEDS	Gastrointestinal			Nervous Irritability			α-La	β-Lg
					GER	Colic	Diarrhea					
1	16	M	Casein	+	-	-	+	+	26.0	3	0	1
*2	3	M	Casein	-	+	+	+	-	4.0	3	3	1
3	6	M	Casein	+	-	+	-	+	195.0	3	0	2
4	6	F	Casein	+	-	-	-	-	66.0	2	0	2
5	9	F	Casein	+	-	-	-	-	74.0	4	2	1
6	6	M	Casein	+	+	-	-	+	257.0	2	1	0
7	24	M	Casein	+	-	-	-	-	5000.0	2	1	0
8	14	F	Casein	+	-	-	-	+	2633.0	4	0	1
9	28	F	Casein	+	+	-	+	-	12.0	3	0	3
10	7	M	Casein	-	+	-	-	+	2.0	3	2	0
11	11	F	Casein	+	+	-	-	-	342.0	ND	ND	ND
*12	18	M	Casein	+	-	-	-	-	177.0	4	3	2
13	6	M	Casein	+	+	+	+	-	1354.0	2	2	1
14	20	F	Casein	-	-	-	-	+	33.0	ND	ND	ND
*15	6	M	Casein	+	+	-	+	+	141.0	4	2	3
16	10	F	Casein	+	-	-	+	-	149.0	2	2	0
17	28	M	Casein	+	-	-	+	-	2634.0	2	1	2
18	11	M	AAF	+	+	-	-	-	12.0	3	4	2
*19	6	M	Whey	+	-	+	-	+	39.0	2	3	0
20	24	F	Whey	+	+	-	-	-	77.0	1	3	3
21	2	M	Whey	+	+	+	+	+	9.0	ND	ND	ND
22	2	M	Whey	-	+	+	-	+	50.0	ND	ND	ND

AAF – amino acid-based formula; ND – not done; α-La – alfa-lactoalbumin; β-Lg – beta lactoglobulin; * – children with hypersensitivity to both hydrolysates

treatment of cow's milk protein allergy and are well tolerated by 90% allergic children [9,11-13]. In recent times there have been increasing reports of intolerance to hydrolysates in infants and young children [14-16]. Allergy to extensive hydrolyzed formula may be part of more severe syndrome, multiple food allergy (MFA) in highly allergic children. According to Sampson et al.,

8-10% of CMA children have hypersensitivity to casein [17]. In our study hypersensitivity to casein or whey proteins or both was found in 32.8% of AEDS children. In retrospective study by Latcham et. al, 43 of 121 (36%) children with multiple food allergy had intolerance to standard cow's milk hydrolysate formulas and did well with an amino acid formula (Neocate) [18]. In the

Figure 8. Mean time of breast feeding in AEDS children with or without hypersensitivity to hydrolysates (HHF) (n=67)



presence of allergy to other foods, tolerance of eHF and of CM occurs later and a restricted diet based on AABF is required for a longer duration [14].

The skin is one of the target organs involved in food hypersensitivity reactions. The most recent studies have shown that the IgE response after allergen-induced mast cell activation is characterized by skin infiltration of monocytes and lymphocytes [19]. Although eosinophils are not predominant in histologic sections of AEDS lesions, as seen in allergen-induced asthma, immunohistochemical staining of AEDS skin has revealed prominent deposition of eosinophil major basic protein and eosinophil-derived neurotoxin in active eczematous lesions [20]. Major basic protein is a cytolytic protein secreted almost exclusively by eosinophils capable of damaging skin epithelial cells and promoting mast cell degranulation and its deposition is not found in uninvolved skin sites. We have studied plasma eosinophils and higher number of these cells indicates an active allergic component in AEDS children with HHF.

The potential antigenicity and allergenicity of hydrolysates is caused by residual immunologically active protein and its immunoreactive epitopes. Residual allergenic activity has been described in partially and in extensively hydrolyzed formulas and indicates that technological separation of casein from whey proteins is unsatisfactory and it may cause anaphylactic reactions in sensitized children [21].

Accepting that none of hydrolysate-based products is completely safe, the American Academy of Pediatrics (AAP), the European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) and the European Society of Paediatric Allergy and Clinical Immunology (ESPACI) recommend that introduction of these formulas in CMA children should be carried out under a doctor's supervision and tested in double DBPCFC [22]. As indicates our study children with AEDS accompanied by CMA are highly predisposed to hypersensitivity reactions to hydrolysate-based formulas, but randomized study is necessary to verify these results.

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