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Evaluating the Clinical Efficacy of a Highly Hydrolyzed Casein Formula in Diet Therapy of Severe Forms of Cow's Milk Proteins Intolerance in Children

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The most common food allergies in young children are caused by various fractions of cow's milk proteins. Given the important role of cow's milk as a dairy component in the diet of children during the first years of life, the therapeutic diet is based on specialized products – cow s milk protein hydrolysates. The authors of the study conducted an assessment of the clinical efficacy of highly hydrolyzed casein formula. 46 children aged 12.2 months with a moderate (SCORAD ≥ 20) or severe (SCORAD ≥ 50) index of food allergy manifestations had been given the product. 73% of the surveyed children were diagnosed with an increase in IgE in the blood serum by 5-10 times at the beginning of the study. As a result of the study, 96.2% of children showed improvements of skin manifestations, reduction of IgE level, including 68% of children who had achieved clinical remission.

Keywords*: infants, first year of life, allergy to cow's milk protein, diet, highly hydrolyzed casein formula.*

Food allergy (FA) is one of the most important problems of current pediatrics and child allergology. Intolerance to cow's milk proteins is the cause of this condition in early childhood and its frequency in the population is about 2-3% [1-3]. Despite the fact that clinical tolerance is formed by milk proteins in children up to 3 years of age in the majority of cases, a certain percentage of the children's FA doesn't disappear completely and becomes the debut of "allergic march" [4, 5]. Diet

therapy is the basic treatment of FA in children, along with drug and local skin therapy [6-8].

Partial hydrolysates of whey proteins, known as HA formulas (i.e., hypo-allergenic ones), are widely used in the prevention of allergic diseases in children [9, 10]. They are recommended for children at high risk for the development of atopic and they are prescribed in mixed or bottle feeding of the child in the absence of clinical manifestations of FA [11, 12]. In mild or moderate forms of FA in children high hydrolysates whey proteins formulas are usually the products of choice. In severe forms of FA (a common atopic dermatitis, anaphylactic shock), specialized blends of high casein hydrolysates are recommended, which have the highest clinical efficacy [13, 14]. Casein fraction of cow's milk protein has a higher degree of hydrolysis compared to whey proteins. In addition, the caseins have less allergenic potential than whey proteins.

A clinical trial of highly hydrolyzed casein formula “Frisopep AC” (Friesland Campina, the Netherlands) in infants with food allergy was conducted in the Research Center of Children's Health, RAMS, in accordance with the principles of Good Clinical Practice (1991), which represented an open, longitudinal, prospective medical surveillance.

The criteria for selecting children for the clinical trials were:

• Age of the children from 1 month to 1 year old;

• Presence in patients moderate (SCORAD ≥ 20) or severe (SCORAD ≥ 50) atopic dermatitis, with sub acute or acute degree course, and / or gastrointestinal manifestations of food allergy, confirmed by an allergy to cow (PCM) / goat milk proteins.

The exclusion criteria were:

• Presence of infectious diseases during clinical trials;

• Lack of positive effect or deteriorating while taking product within 2-4 weeks.

The study included at least three visits, communication through phone; if necessary, patients were hospitalized by indications. The duration of follow-up was 12 weeks.

Formalized Medical history and list of record SCORAD (severity scale score of atopic dermatitis) were instituted for all participants; informed consent from the parents of the children to participate in the study were obtained.

Allowable therapy was: sorbents, antihistamines, enzymes, pre-and probiotics, local skin therapy.

List of unauthorized drugs and food included: systemic corticosteroids and any products containing cow's milk protein, goat milk, soybeans; products that were hypersensitive to the patient and any other formulas of highly or partially hydrolyzed milk protein.

In order to conduct a clinical trial of the product a examination scheme of children was used, which included the following options:

- Assessment of physical development parameters: weighing - 1 time per week during the study by using standardized scales; measure the length of the body - at the beginning and the end of the study by using a standard stadiometer;

- General clinical assessment of children's health (general condition, emotional tone, appetite, sleep, physical examination results, etc.);

- Evaluation of the skin and the dynamics of skin lesions (pruritus, sleep disturbance, etc.) on a SCORAD scale;

- Assessment of gastro-intestinal tract symptoms and signs;

- Assessment of the dynamics of immunological indices, clinical blood and urine tests, scatology.

Prescription of a formula

With the introduction of the product the below rules were followed:

- Complete replacement of milk (or soy) component in a health plan;

- Gradual introduction of the formula, starting with 10 ml each feeding on the first day, then increasing the product by 30-60 ml daily at each feeding until the required volume; a complete transfer to the new formula for 5-7 days;

- A new blend was given only with a single bottle, without mixing it with displaced product;

- Change of feces color to a greenish-gray was permissible; it was not a cause for cancellation of the formula.

Medical therapy

In accordance with the protocol symptomatic drug therapy was administered to children with changes in stool characteristics, ultrasound data, and immunological

parameters of blood. Sorbents (Enterosgel, Laktofiltrum), enzymes (Creon, Mezim forte), prebiotics (Hilak forte), probiotics (Linex, Primadofilus), external treatment (Fukortsin, Bepanten, Elidel, etc.) were used. Antihistamines (Zirtek, Fenistil) were administered in cases of severe dermatitis or skin itching.

Characteristics of the Frisopep AC specialized formula

The investigated formula is a dry product of highly hydrolyzed casein developed for therapeutic feeding of children from birth to 24 months. The product contains casein hydrolyzes, vegetable oils (sunflower, palm oil, rapeseed oil), carbohydrates (glucose syrup), enriched with vitamins, macro-and micronutrients, taurine, choline, and L-carnitine.

The structure of the protein component is mostly comprised by amino acids and proteins with low molecular weight - less than 1, 5 kD, and a low proportion of high-molecular fragments - more than 6, 0 kD (Table 1).

The composition of the product is given in Table 2.

As shown in Table 2, therapeutic blend made of high hydrolyzed casein, is a modern, specialized product that meets the requirements of the Russian Federal Law from June 12, 2008 № 88-FZ "Technical regulations on milk and dairy products" and "Single sanitary-epidemiological and hygienic requirements for the goods suspected for sanitary-epidemiological supervision (control), approved by the decision of the Custom Union Commission on May 28, 2010 № 299 for this type of infant food.

The results of the tasting demonstrated that the studied mixture has a creamy white color, milky smell and bitter taste, typical for products containing hydrolyzed milk protein.

Characteristics of the surveyed children

46 children aged 2 to 12 months received this therapeutic formula. The average age of patients was 6.1 months. All infants had severe or moderate atopic dermatitis. By the beginning of the study, all children had had skin manifestations of food allergy in a common form of atopic dermatitis: 26 (56.5%) infants had severe course (SCORAD> 60), and they were the group III, 16 ones (34.7%) had moderate with (SCORAD> 20 <60) acute phase of the disease (Group II). 4 (8.6%) infants had moderate atopic dermatitis with skin condition as consistent with an incomplete clinical remission (SCORAD <20) - Group I (Table 3).

Elevated levels of specific immunoglobulin Ig E to the milk proteins and its fractions (grades 1-3 reactions) were revealed in all cases during the allergy examination (Table 4).

The majority of patients (97.9%) showed a significant skin improvement during the course of the treatment. Exacerbation of atopic dermatitis was observed in only one child with a high degree of sensitization to cow's protien, including the casein fraction, so that the patient was excluded from the study.

Assessment of the actual meal plan and physical development of children having this product showed that a diet was consistent with their physiological needs (Table 5), and average daily weight gain did not differ from that in healthy children (Table 6).

It is important to note that the improvement of the skin has already started on the 1-2nd week at the beginning of the formula feeding . By the 4th week of therapy the incidence of skin lesions was significantly reduced: itching had reduced more than 5 times and as well sleep improved. The intensity of the skin process was significantly reduced: the severity of erythema was decreased and exudation was stopped completely. The partial clinical remission has arisen in 37 (82.2%) children out of 45 observed , and 5 (11.1%) had a marked tendency toward improvement, only 3 had remained moderate manifestations of atopic dermatitis. The average SCORAD index observed in children has decreased by more than 3 times and equalled to 18.4 vs. 59.8 prior to treatment. The dynamics of the intensity of the cutaneous manifestations are shown in Table. 7.

Skin condition continued to improve, and exacerbation of atopic dermatitis were not noted in any case in 3-4th months of observation. By the end of the observation period (5-6 months), all patients were in stable clinical remission. Mild manifestations of atopic dermatitis persisted in 14 (31.1%) children, and the area of damage was not more than 5-10%, the majority of (31, 68.9%) observed patients with allergic skin didn't have any skin changes. SCORAD index decreased by 89.1% by the end of the study and was 6.5 versus 59.8 points before the application of the product. Sleep normalized in patients with a decrease of pruritus.

The level of total Ig E has not increased in patients receiving treatment product, 30 (68%) children have showed a decrease of sensitivity to cow's and goat's milk proteins to the first class of reactions. Retesting with "ELISA Lakttest" was held on 7 children, without any increase of IgE serum antibodies towards protein-peptide fractions of the formula.

The level of total IgE in patients receiving Frisopep AC has not increased, 30 (68%) children have showed a decrease of sensitivity to cow's and goat's milk proteins until Class I-III reactions, 5 (12%) -to the soy protein until class I-II reactions.

According to the abdominal ultrasound examination, most children (68%) had symptoms of reactive pancreatitis, the size of the pancreas has been normalized during diet therapy.

Stool characteristics in the dynamics (3 months) showed a good digestibility and assimilation of the product, which manifested as the absence of high content of fiber, neutral fat, iodophilic flora, mucus, and leukocytes in feces. Children with normal stool had no change with the formula feeding. The stools returned to normal after 5-7th day of administration of therapeutic formula in patients with unstable character of the stool and with a partial lactase deficiency. No child had increased excretion of lactose in the feces upon double check up.

While following a diet all children were consistently introduced products of hypoallergenic foods (dairy-free cereal, vegetable, meat and fruit puree.) The level of hemoglobin in children with iron deficiency increased to 110 g / l after 3 months of dietary treatment.

Conclusion

Results of clinical studies of a highly hydrolyzed casein formula indicate that Frisopep AC meets current requirements applied to the composition and performance of specialized products for therapeutic feeding of children with severe manifestations of allergy to cow's milk proteins.

High efficiency of this diet is confirmed by stable positive dynamics of the skin and gastrointestinal manifestations, physical development, immunological blood indexes, stool characteristics and other laboratory data.

Table 2 shows the composition of casein hydrolysate formula at the time of the study. Recently the product composition has got some changes, in particular nucleotides have been added, which have immune modulatory effects.

The studies can appreciate the quality, safety and clinical efficacy of a highly hydrolyzed protein formula in atopic dermatitis of varying severity, caused by food and / or polyvalent allergy, and it is advisable for its prescription with this type of pathology in infants and young children.

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Table 1 Molecular weight distribution of peptide fractions

in a hypoallergenic therapeutic blend

Particles' size (kD)	Percent of distribution
Free amino acids and peptides less than 1,5 kD	94,2
1,5–3,5	5,5
3,5–6,0	0,16
More than 6,0	0,14

Table 2 Chemical composition and energy content of a specialized formula

Frisopep AC

Ingredients	Unit	Content	
		In 100 g of dry product	In 100 ml of ready for usage product
Protein(Casein hydro lysate)	g	11,7	1,5
Fat Linoleic acid α-Linolenic acid Linoleic acid /Fat acid, %	g g mg	27 3400 485 14	3,5 440 63
Carbohydrates Glucose syrup	g g	55,7 55,7	7.2 7.2
Minerals			
Calcium	mg	515	67
Phosphorus	mg	330	43
Iron	mg	5,2	0,68
Copper	мкг	375	49
Sodium	mg	225	29
Potassium	mg	600	78
Chloride	mg	335	44
Magnesium	mg	46	6,0
Zink	mg	4,6	0,60
Iodine	мкг	54	7,0

Manganese	мкг	365	34
Selenium	мкг	7,0	0,91
Vitamins			
Vitamin A	ug-RE	495	64
Retinol	ug-RE	445	58
Beta-carotene	mg	310	40
Vitamin D3	CIM	9,3	1,2
Vitamin E	mg	10	1,3
Vitamin K_1	mcg	38	4,9
Vitamin B_1	mcg	335	44
Vitamin B_2	mcg	700	91
Niacin	mcg-NE	7400	960
Vitamin B_6	mcg	300	39
Folic Acid	mcg	80	10
Pantothenic Acid	mcg	1730	225
Vitamin B_{12}	mcg	0,8	0,10
Biotin	mcg	8,5	1,1
Vitamin C	mg	65	8,5
Taurine	mg	35	4,6
Choline	mg	60	7,8
L-carnitine	mg	12	1,6
Inositol	mg	115	15
Osmolarity	mOsm/l	+190	
Energy value	kal	515	67

Table 3.Clinical characteristics of observed infants

The disease, a form	**The age distribution**			
	4−6 mo.	**7−12 mo.**	**Total**	**%**
Atopic dermatitis, moderate form, partial remission, SCORAD ≤ 20 Group I (n = 4)	0	4	4	8,7
Atopic dermatitis, moderate form, exacerbation period, SCORAD> 20 ≤ 60 Group II (n = 16)	4	13	16	34,8
Atopic dermatitis, a severe course SCORAD> 60 Group III (n = 26)	6	20	126	56,5
Total	10	36	46	100
Comorbidities				

Lactase deficiency	5	2	7	15,2
The consequences of cerebral ischemia 3	3	11	14	30,4
I degree malnutrition	-	6	6	8,7
Iron deficiency anemia I grade	5	2	7	15,2
Dysfunction of the gastrointestinal tract	7	6	13	28,3

Table 4 The incidence of specific IgE to cow's milk proteins, its factions and to goat's milk protein in infants with food allergy (n = 46)

Immunoglobuline-bowline (class of reactions)	**CTW**		**BSA***		**Casein**		**β-N****		**Goat's milk**	
	n	%	n	%	n	%	Abs.	%	Abs.	%
1	14	31,0	8	17,2	6	13,8	8	17,2	13	29,3
2	6	12,0	3	6,9	1	1,7	1	1,7	2	5,2
3	4	8,6	5	10,3	0	0	0	0	4	8,6
Total (1−3 grade)	24	**52,2**	16	**34,8**	7	**15,2**	9	**19,6**	19	**41,3**

Notice: CTW - cow's milk protein * - bovine serum albumin; ** - β-lactalbumin.

Table 5. The content of major nutrients and energy value of the average daily dietary treatment using a mixture

Daily diet / The basic needs	**Food ingredients g/kg**			**Energy value, kcal/kg (M ±m)**
	Protein (M ±m)	**Fat (M ±m)**	**Carbohydrates (M± m)**	

A diet with a mixture of AC Frisopep	2,9±0,8	6,0±0,5	12,0±0,2	114± 0,2
Age requirements *	2,2−2,9	5,5−5,6	13	110−115

Notice * - Standards of physiological requirements for energy and nutrients for different groups of children in the Russian Federation, Guidelines (MR 2.3.1.2432-08) approved by the Chief Sanitary Doctor of Russia, G.G. Onishchenko 18.12.2008.

Table 6 The average weight gain observed in children with atopic dermatitis treated with Frisopep AC

Indicators	**Age of children(mo.)**	
	4−6	**7−12**
The average weight gain observed in children (g / mo.), M ± m	564±68	430±124
Physiological average weight gain (g / mo.)	700−400	500–300

Table 7 The dynamics of value SCORAD index in children with atopic dermatitis treated with Frisopep AC

Groups	**Number of children**	**Index SCORAD**	
		At the beginning of the observation (M ± m)	On the background diet (M ± m) *
Group I	4	12,5±4,2	0
Group II	16	42,9±7,1**	5,3±2,3**
Group III	26	83,1±8,7**	9,7±2,2**

Notice: * - After 1-1.5 months of starting treatment; ** - p <0.01