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Original research article/Artykuł oryginalny

Clinical effectiveness of amino acid formula in infants with severe atopic dermatitis and cow's-milk protein allergy

Skuteczność kliniczna mieszanki aminokwasów u niemowląt z ciężkim atopowym zapaleniem skóry i alergią na białko mleka krowiego

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ARTICLE INFO

Article history:

Received: 23.05.2016

Accepted: 05.07.2016

Available online: 21.08.2016

Keywords:

- Food allergy
- Atopic dermatitis
- Diet therapy

Słowa kluczowe:

- alergia pokarmowa
- atopowe zapalenie skóry
- leczenie diety

ABSTRACT

Introduction: The incidences of food allergies and related allergic diseases have been increasing in the recent years. **Objective:** The aim of this study is to evaluate clinical effectiveness of dietary intervention with amino acid-based formula (AAF) containing 100% free amino acids in the management of severe CMP allergy and atopic dermatitis (AD). **Material and methods:** Thirty infants aged from 29 days to 11 months with severe AD (Eczema Area and Severity Index [EASI] score >18) and confirmed CMP allergy were enrolled into the study. Twenty two patients have completed the study. The evaluation AAF's clinical effectiveness was carried out on the 7th, 14th and 28th day after reaching the full daily feeding volume. **Results:** In infants with severe AD (EASI score >18) the involvement of several organs and systems into the pathological process was typical: i.e. in 68% of the cases the skin symptoms were combined with the impaired function of the gastrointestinal tract and changes in the frequency of bowel movement (constipation, diarrhea), appearance of pathological admixtures in feces (mucus, blood), vomiting, etc. Feeding with AAF was associated with reliable reduction of severity not only of isolated skin (98%) but of combined skin and gastrointestinal manifestations of food allergy (82% of the cases). The formula was well tolerated by infants with severe AD and may be used for exclusive feeding of babies with severe CMP allergy. **Conclusions:** The

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<http://dx.doi.org/10.1016/j.pepo.2016.07.003>

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described positive treatment effects were obtained with the diet duration of 4 weeks, the optimal period for the elemental diet administration needs further investigation.

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Introduction

The incidences of food allergies and related allergic diseases have been increasing in the recent years. This is especially noticeable in developed countries in families with high socioeconomic status [1]. Clinical symptoms of allergic reactions which are mainly related to the peculiarities of nutrition could already be observed in infancy [2].

Food allergy in infants and toddlers is mainly represented by immunological response to one or more cow's milk proteins (CMP) [3]. Its exact prevalence in infants is unknown, approximately ranging from 2 to 6% [4–6]. Clinical manifestations of CMP allergy decrease or disappear at the end of the first year in almost half of the affected children, and in nearly 80% of the cases within the first 3 years of life [7, 8].

According to Emilia-Romagna working group on Allergology and the Working Group on Children's Gastroenterology (EWGPAG), CMP allergy occurs in 2–6% of children with the greatest prevalence during the first year of life [6]. Australian scientists reported that CMP allergy is manifested in 2% of young children [4]. According to recent studies in Japan, the prevalence of allergy to CMP is 0.2% in newborns and 0.35% in preterm babies with birth weight less than 1000 g [9]. Most of the authors estimate the prevalence of CMP allergy in infants and toddlers at the level of 5–8%, in adults – 1–2% [10–12]. According to American authors, among the 28% of young children with the likely clinical manifestations of food allergy, controlled oral food challenge confirmed the diagnosis of CMP allergy only in 8% of the cases [13].

Epidemiological data on the incidence of CMP allergy, confirmed with controlled oral food challenge, are mainly based on the following five studies:

1. In Denmark, 1749 children of the first year of life – 2.2% [14].
2. In Finland, 6209 babies aged less than 15 months – 1.9% [15].
3. In Norway, 193 preterm babies and 416 term infants under the age of 6 months – 4.9% [16].
4. In the UK, 969 infants – 2.16% [17].
5. In the Netherlands, 1158 infants – 2.24% [18].

Epidemiological data on the incidence of CMP allergy in Ukraine require clarifications and additional studies.

According to the pooled data, CMP allergy is clinically manifested by skin symptoms in 5–90% of the cases, gastrointestinal symptoms – in 60%, respiratory symptoms – in 19–30% and anaphylaxis – in 0.8–9% of the cases [19]. Clinical symptoms of CMP allergy vary from mild to moderate and severe.

Analysis of etiological spectrum of food allergies in infants and toddlers indicates that CMP belongs to one of three major allergens, but in all the countries where researches were carried out, CMP was the second leading

cause of food allergy after egg allergens [19]. Peanut allergens (the United States, Switzerland), wheat (Germany, Japan), fish (Spain) or sesame (Israel) placed third among the major allergens.

However, despite the fact that CMP allergy is not the most common type of food allergy, it represents a significant problem because we cannot simply eliminate milk from the infant's diet like we do it with any other cause-significant allergen in the case of food allergy of another origin or in the early treatment of any other allergic disease.

Infancy is characterized by the highest rates of physical and psychomotor development. Such intensive plastic processes require an appropriate supply of energy, food ingredients, biologically active substances, the need for which is the greatest (per kg of body weight) compared to all other periods of child development. The said intensive development occurs on the background of functional immaturity of the main enzymatic systems of the gastrointestinal tract and under the conditions of evolutionary formed exclusively lactotrophic nutrition. Elimination of milk from infant's diet is not an issue, but another question is what should be fed to the baby? Only milk or dairy products contain all the necessary nutrients, and only milk is a proper physiological product for baby's first months of life.

On the other hand, if we do not eliminate a cause-significant allergen, sensitization will increase with the likely formation of severe forms of allergic diseases. CMP is the first food allergen to which all bottle-fed infants and many breastfed infants are exposed. So called 'atopic march' begins from CMP allergy with gradual extension of the sensitization range and change of the target organ: AD, bronchial asthma, allergic rhinitis. Not only the infant's physical growth and anatomical-physiological properties of all organs and systems, but a whole scenario of atopic march development throughout life depend on physician's competency in the management of a patient demonstrating the first clinical signs of sensitization to CMP with the possibility of its modification and improvement of the prognosis.

For several decades scientists have worked on the problem of CMP allergy during infancy. The evidence for this is not only hundreds of publications and creation of the new feeding products – that is, milk formulas with extensively hydrolyzed protein, but first of all in the development of International Guidelines devoted to CMP allergy. There are no such separate guidelines for any other allergen. On the other hand, CMP allergy guidelines cover the specific allergy issue, not a particular disease, which indicates exceptional global importance of the problem. The key guidelines created on the basis of evidence-based medicine and reflecting the achievements in solving the said problem are as follows: 'Diagnostic Approach and Management of Cow's-Milk Protein Allergy in Infants and Children: ESPGHAN GI Committee Practical Guidelines' (2012) [20], 'World Allergy Organization (WAO) Diagnosis and Rationale for

Action against Cow's Milk Allergy (DRACMA) Guidelines' (2010) [19], 'Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel' (2010) [5], 'Management of cow's milk protein allergy in infants and young children: an expert panel perspective' (2009) [4], 'EWGPAG. Cow's milk protein allergy in children: a practical guide' (2010) [6]. It should be emphasized that this problem has also been studied and discussed in Ukraine. The results of these studies were laid down in 'Clinical recommendations on management food allergy to cow's milk protein' approved at an open international Congress of Pediatric Gastroenterologists and Nutri-
ciologists of Ukraine (Lviv, 2012) [21].

The recommendations of the current guidelines are clearly the same: if CMP allergy is diagnosed, the elimination of the causal allergen is mandatory. But we cannot simply remove CMP from the infant's diet – we have to change it as a whole. The best replacement of regular infant formula containing CMP is only a formula with extensively hydrolyzed CMP (EHF) or an amino acid-based formula (AAF). In most cases EHF is effective in the treatment of the diseases with CMP allergy in their pathogenesis [19, 20]. Nevertheless, in some patients this type of formula is ineffective. Such patients usually have the most severe forms of the disease with continuous recurrent course and development of immunopathological reactions even in spite of feeding with special EHF. The only way to help such babies is to use AAF. This type of special care formulas only recently has become available for Ukrainian children.

Despite the relatively long history of AAF's use in the developed world, there are still many unresolved scientific and practical issues. From the scientific point of view the effectiveness of the AAF in the management of severe AD requires further investigation because only a few collective studies devoted to this issue have been carried out so far. From the practical standpoint, it is vital to provide Ukrainian pediatricians and pediatric allergologists with an experience of the formula use in our circumstances.

Aim of the study

The aim of the study is to evaluate the clinical effectiveness of the amino acid-based formula (AAF) in infants with severe atopic dermatitis (AD) and cow's-milk protein (CMP) allergy.

Material and methods

Thirty formula-fed infants aged from 29 days to 11 months with severe AD and confirmed CMP allergy (an open controlled food challenge) were enrolled into a prospective multicenter study. The diagnosis AD was done according Ukrainian recommendations, based on Hanifin, Rajka criteria [22, 23]. An open controlled food challenge was performed under the standard procedure [19, 24]. In 5 of the children (17%) the lack of effect from the previous diet with EHF had been reported.

The study inclusion criteria were as follows: AD severity based on Eczema Area and Severity Index (EASI) score >18,

medical history data suggesting the development of CMP allergy, positive result of an open controlled food challenge and an informed consent of both parents [25]. The exclusion criteria were the following: the presence of AD complications (bacterial, fungal infections of the skin, lymphadenopathy, etc.), congenital anomalies, any chronic disease (including primary immunodeficiency syndrome, disorders of metabolism) or acute illness; use of any other food products apart from the AAF or the need for treatment with systemic corticosteroids. Twenty two infants completed the study, having been fed with AAF for 4 weeks. Eight babies were excluded from the study because of the failure to comply with the study protocol requirements. The study involved four centers of Ukraine (Kyiv, Lviv, Kharkiv and Zaporizhzhya).

In the course of the study all the infants were fed with the special AAF 'Nutrilon Amino' (Nutricia, Holland) which contains 100% free amino acids and is designed for adequate infant nutrition from birth. The formula was administered gradually, reaching 100% of the daily volume for 3 days. After that the AAF was administered during 4 weeks in an amount that corresponded to the infants' needs. The evaluation of clinical effectiveness of the diet was carried out on the 7th, 14th, and 28th day after reaching the full daily volume of the formula according to the predefined evaluation criteria. An open controlled food challenge with the EHF 'Nutrilon Pepti' (Nutricia, Holland), containing extensively hydrolyzed whey protein, was performed on the 28th day after reaching the full daily volume of the AAF with the evaluation of immediate type (for 2 h after the completion of the challenge under medical observation) and delayed type (after 72 h – on the 31st study day) of immune reactions. An open controlled oral food challenge with EHF was performed under the procedure, used for challenge with cow's milk.

Six medical investigations which, along with a comprehensive physical assessment, involved an evaluation of the growth parameters, severity of AD, the effectiveness of dietary interventions and the results of the food challenge were carried out during the study period.

The severity of AD was evaluated with the EASI and SCORAD scores. The degree of skin symptoms severity was estimated in the area of maximum impact. The overall effectiveness of dietary interventions was estimated with a special 10-point subjective analog scale (0 – lack of the effect, 10 – maximum effect) separately, according to doctor's and parents' opinions. Parents assessed the effectiveness of the dietary interventions (disappearance of gastrointestinal symptoms, alleviation of skin symptoms, etc.) once a week. A doctor recorded the result of parental evaluation into an observation diary, which was filled during the visit. Doctors also simultaneously assessed the effectiveness of the treatment of all infants every time they visited with the same 10-point scale.

Infants' growth was evaluated with the WHO growth curves [26].

The local therapy of severe dermatitis included topical corticosteroids class I-III of activity administered in accordance with clinical indications and age restrictions, as well as appropriate moisturizing agents. The areas of secondary

infection were cured. In the presence of severe exacerbations and the localization of the lesion on the skin of trunk and limbs initial treatment was carried out with third class topical corticosteroids. Sensitive skin areas (neck, folds etc.) were cured with class I corticosteroids. In the case of localization of the lesion on the skin of trunk and limbs topical corticosteroids class I-II were used. Infants involved into the study did not receive prolonged systemic therapy with corticosteroids. Antihistamine medications were used as indicated.

Statistical analysis

The standard methods of descriptive, one group nonparametric comparison statistics and correlation analysis were used as appropriate. The data with normal distribution are presented as a mean value (SD), in the case of nonparametric distribution the data are presented as a median value [interquartile range]. The changes of the 10-point scale score were evaluated with nonparametric Wilcoxon matched pairs test. The differences were considered statistically significant if the alpha-error was less than 5% ($p < 0.05$).

Results

According to the criteria of study enrollment all the 22 infants (13 boys and 9 girls) were born on term with normal birth weight and length (average birth weight was 3458.64 (464.064) g and birth length – 52.14 (2.38) cm). Apgar scores in the all patients were above 7. Most of the infants (19–86%) were attached to maternal breast within the first hour of life.

Most of the infants' mothers involved into the study had higher (13–59%) or incomplete higher (3–14%) education. As for fathers, the percentage was 55% and 5% respectively. Seven fathers (32%) had secondary vocational education. Most of the mothers (15–8%) at the time of the study were on maternity leave, two (9%) continue their education and two (9%) worked. Most of the fathers (19–86%) worked.

Four children (18%) were born after complicated pregnancies. The course of labor and delivery was complicated in three cases (14%), five infants (23%) were born with cesarean section. Eight (36%) mothers and seven (32%) fathers had complicated allergic history. In one case both parents had allergic symptoms in the past. Four (18%) mothers followed the elimination diet during pregnancy. Infants had been breastfed, on average, for 6 [2, 12] days (Table I).

The first skin signs of AD appeared in an average age of 4.5 weeks. The onset of AD was often associated with the beginning of formula feeding (11 cases – 50%) or consumption by mothers who breastfed their babies, of potentially allergic food (9 cases – 41%). In nine children (41%) the presence of allergic disease has been initially suggested by the increased concentrations of specific and total serum IgE (Table I).

In most of the cases the disease has been characterized by continuous recurrent course and insufficient efficiency of the diet and the other treatment measures. Before

Table I – The characteristics of the infants involved into the study

Parameter	Value
Number of boys/girls	13/9
Birth weight, g	3458.64 (464.064) ^a
Birth length, cm	52.14 (2.38) ^a
Duration of breastfeeding, days	6 [2, 12] ^b
Age at the disease onset, weeks	4.5 [4.0; 9.0]
Age at the beginning of the study, months	5 [3; 9]
Increased specific serum IgE	9 (41) ^c

^a Mean (SD).

^b Median value (interquartile range).

^c The number of cases (%).

enrollment into the study five infants (22%) received EHF, ten (45%) were fed with hypoallergenic formula containing only partially hydrolyzed protein and seven (33%) were fed with standard infant formula. Four infants (18%) were treated with class II topical corticosteroids and seven patients (32%) with class III corticosteroids. Anti-inflammatory therapy with other medications was carried out in seven infants (32%). Moisturizing agents were used in the all patients. Most children also received antihistamine and probiotic preparations (16 cases – 73%), 17 patients (77%) – enterosorbents, 10 patients (45%) – enzymes, and 6 patients (27%) – hepatoprotectors.

Treatment with the AAF was initiated at the infants' age of 5.5 (2.3) months. Severity of AD based on average EASI score at this point was 34.49 (13.59).

Administration of the AAF was satisfactory tolerated by the majority of patients, however, it caused vomiting in one child (5%), was accompanied by symptoms of diarrhea in 5 (23%) infants, constipation – in 8 (36%), and appearance of mucous admixtures in feces of 4 children (18%).

At the same time, with an introduction of the new diet positive changes in growth parameters were seen almost in all patients (Fig. 1). Average monthly increments of body weight and length in infants included into the study were 500 (300; 700) g and 1.0 (1.0; 3.0) cm respectively. Only in 3 patients with very severe AD weight increased only by 50–150 g, and in other two infants, during the study period length increased by 0.4 cm and 0.5 cm.

At the end of the study no child had weight or length deficit for their age taking into account the appropriate Z-indexes. At the same time, unlike the weight Z-indexes

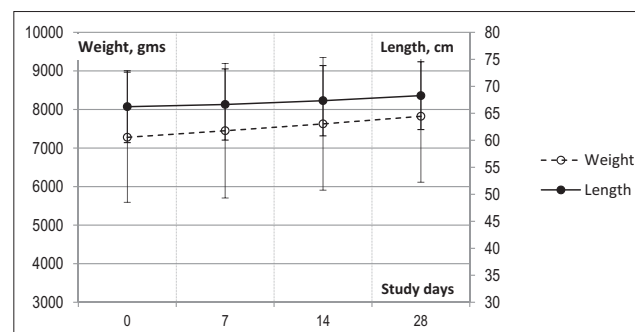


Fig. 1 – Changes of weight and length in infants during the study

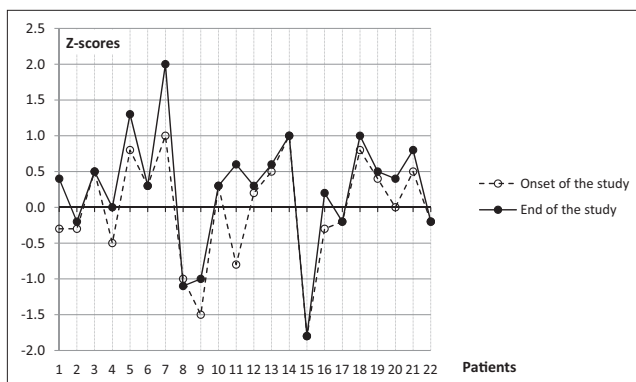


Fig. 2 – Aged body weight Z-scores at the beginning and at the end of the study

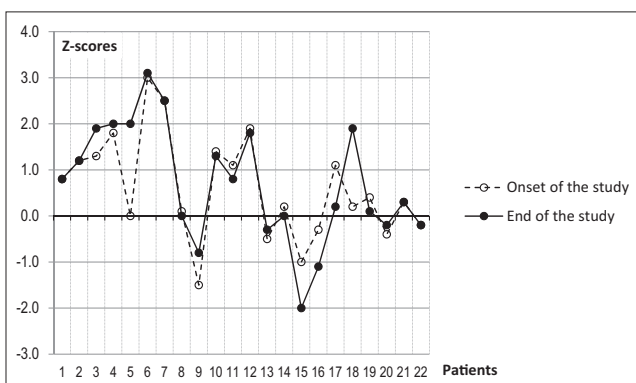


Fig. 3 – Aged body length Z-scores at the beginning and at the end of the study

which unchanged or increased in all but one infant (Fig. 2), the Z-indexes for length in 9 infants (41%) decreased (Fig. 3) but nonetheless did not exceed the normal limits. There was no reliable correlation between AD severity based on

the EASI/SCORAD scores at any point of the study with weight or length changes in the course of the study period.

Already in one week after the administration of the AAF in its full daily volume the reliable decline of the EASI and SCORAD scores was detected (from 32.16 (12.6) to 14.98 (9.92), $p < 0.001$, and from 71.23 (11.43) to 47.086 (16.76), $p < 0.001$, respectively). By the end of 28-day treatment course the scores fell to 1.46 (1.31) and 14.18 (6.17) respectively (Fig. 4).

At the onset of the study, in addition to skin lesions 6 (27%) infants had symptoms of diarrhea without increase in body temperature, 5 (23%) – vomiting, 7 (32%) – constipation and 8 (36%) – intestinal colic. Nine infants (41%) had at least one of the problems, three (14%) – 2 problems, three (14%) – 3 problems, and 7 patients (32%) had no gastrointestinal disorders.

After 28 days of feeding with AAF in its full daily volume only one child (5%) still had intermittent vomiting (not more than 2 times during the last week) and three infants (14%) had signs of constipation. Eighteen patients (82%) had no gastrointestinal disorders.

According to the results of correlation analysis, the initial severity of AD determined with the EASI and SCORAD scores on the day of reaching a full daily AAF volume, was not reliably associated with manifestations and severity of gastrointestinal symptoms. However, the severity of AD defined with the EASI scores after 7 special diet days was significantly associated with presence and severity of diarrhea ($R = 0.36$; $p < 0.05$) and vomiting ($R = 0.48$; $p < 0.05$), as well as with parental ($R = -0.77$; $p < 0.05$) and medical ($R = -0.61$; $p < 0.05$) estimates of overall effectiveness of the diet at that point.

The severity of AD defined with the SCORAD scores at the same visit (after 7 special diet days) reliably correlated with the presence and severity of constipation ($R = 0.43$; $p < 0.05$), vomiting ($R = 0.48$; $p < 0.05$) as well as with the parents' evaluation of the diet effectiveness ($R = -0.46$; $p < 0.05$). Infants with more severe AD following the 7-day diet were more likely to continue vomiting ($R = 0.36$;

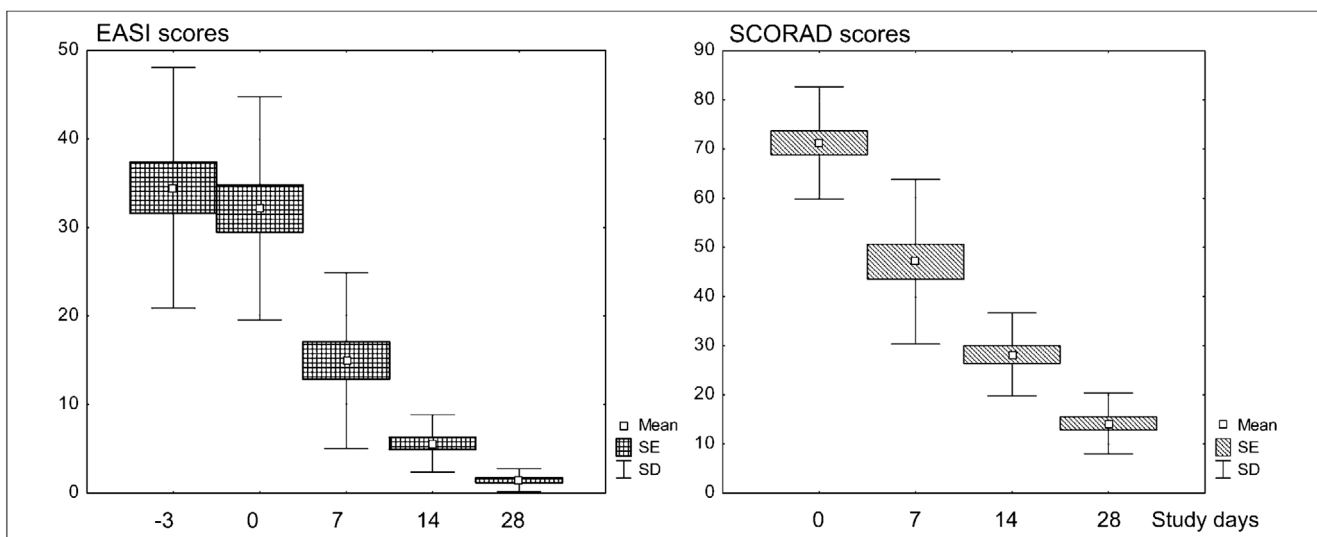


Fig. 4 – Changing in severity of AD during the study period based on the EASI and SCORAD scores ($p < 0.0001$)

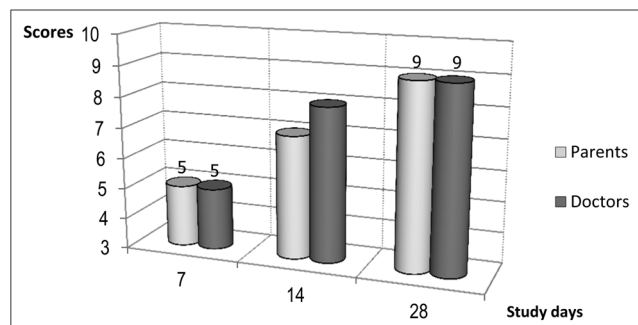


Fig. 5 – Evaluation of clinical effectiveness of the dietary interventions by parents ($p < 0.001$) and doctors ($p < 0.01$)

$p < 0.05$), less likely to have constipation ($R = -0.41$; $p < 0.05$) and more often were considered by doctors as having positive changes after 28 days of the treatment ($R = 0.45$; $p < 0.05$). Obvious reduction of the cutaneous lesions and relief of gastrointestinal symptoms was similarly noted by both groups of respondents: parents and doctors (Fig. 5).

After the completion of the treatment course with the special diet, positive immediate or delayed type of immune reactions to the open oral food challenge with the EHF formula were observed in three infants (14%), making it mandatory to resume feeding with the AAF.

Discussion

As a result of the study we have determined that the administration of amino acid-based formula “Nutrilon Amino” which contains 100% free amino acids to infants with severe AD was associated with reliable reduction of severity not only of isolated cutaneous (98%), but of combined cutaneous and gastrointestinal manifestations of food allergy as well (82% of the cases).

The obtained data are consistent with the results of other clinical studies. In one of those studies, sixteen infants aged 1–16 months who had adverse reactions to CMP and AD symptoms, were prescribed AAF for approximately 1.5 months. In thirteen infants, feeding with AAF induced the disappearance of non-cutaneous symptoms within 3 days and improved eczema (SCORAD: 16 (2) vs 35 (3); $p < 0.05$). All these infants gained weight and an increase in the body weight index at the end of the treatment period was statistically significant [27].

In another study [28] 73 infants with AD (aged 5.7 months on average) were randomly assigned to receive AAF ($n = 31$) or EHF ($n = 42$). A significant improvement was observed in SCORAD in the both groups from a mean value of 24.6 at entry to mean value of 10.7 ($p < 0.0001$) after 6 months. In the AAF group there was a significant increase in the length SD score ($p < 0.04$) despite similar energy intakes, whilst there was no difference in the EHF group.

Over the past 25 years useful experience of AAF use in infants with allergic diseases, including gastrointestinal manifestations of multiple food protein allergy/intolerance

and ineffectiveness of EHF, has been accumulated in many European countries. The positive effect of AAFs was described in studies of Vanderhoof et al. [29], Hill et al. [30, 31] Estep and Kulczycki [32] and others.

Our data as well as the findings of other clinical studies allow us to recommend the inclusion of AAFs into the diet of infants with severe food allergies, including but not limited to AD and allergic gastrointestinal disorders.

Conclusions

This study was the first in Ukraine to investigate the effectiveness of AAF in infants with severe AD and CMP allergy. The obtained results allow to optimize the approaches to complex treatment of this severe disease in infants amid the growing ineffectiveness of traditionally available diets with formulas containing extensively hydrolyzed protein.

For infants with severe AD (EASI score >18) the involvement of several organs and systems into the pathological process is typical: in 68% of our cases the cutaneous symptoms were combined with disorders of the gastrointestinal tract such as changes in the frequency of bowel movement (constipation, diarrhea), appearance of pathological admixtures in excrements (mucus, blood), vomiting, etc.

The administration of amino acid-based formula ‘Nutrilon Amino’ which contains 100% free amino acids is associated with reliable reduction of severity not only of isolated cutaneous (98%), but of combined cutaneous and gastrointestinal manifestations of food allergy as well (82% of the cases). The formula was well tolerated by infants with severe AD and may be used for exclusive feeding of babies with severe CM allergy. The described positive treatment effects were obtained through a 4-week diet, but the optimal period for the elemental diet needs further investigation.

Authors’ contributions/Wkład autorów

SN – study design, data interpretation, acceptance of final manuscript version. ON – data collection. DD – statistical analysis, literature search. Others – according to order.

Conflict of interest/Konflikt interesu

None declared.

Financial support/Finansowanie

None declared.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments invol-

ving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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