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ARTYKUŁ REDAKCYJNY / EDITORIAL PAPER

Mieczysław Chorąży
ZŁOŻONOŚĆ ZJAWISKA ŻYCIA JAKO WYZWANIE DLA MEDYCYNY
COMPLEXITY OF THE PHENOMENON OF LIFE – THE CHALLENGE FOR MEDICINE 251

PRACE ORYGINALNE / ORIGINAL ARTICLES

Alicja Magdalena Stępień-Wałek, Jacek Owczarek, Beata Wożakowska-Kapłon
ASSESSMENT OF RELEASE FACTORS OF B-TYPE NATRIURETIC PEPTIDE DURING THE EXERCISE TEST IN PATIENTS WITH DIABETES AND AFTER MYOCARDIAL INFARCTION WITH PRESERVED LEFT VENTRICULAR SYSTOLIC FUNCTION
OCENA CZYNNIKÓW UWALNIANIA PEPTYDU NATRIURETYCZNEGO TYPU B PODCZAS PRÓBY WYSIŁKOWEJ U BADANYCH Z CUKRZYCĄ ORAZ PO PRZEBYTYM ZAWALE SERCA Z ZACHOWANĄ FUNKCJĄ SKURCZOWĄ LEWEJ KOMORY 261

Nicole Mazur, Aleksander Zarzeka, Filip Dąbrowski, Mariusz Panczyk, Robert Gałązkowski, Joanna Gotlib
OCENA POSTAW LEKARZY WOBEC ROZSZERZENIA UPRAWNIEŃ ZAWODOWYCH PIELĘGNIAREK I POŁOŻNYCH W ZAKRESIE ORDYNOWANIA LEKÓW, WYSTAWIANIA RECEPT I KIEROWANIA PACJENTÓW NA BADANIA DIAGNOSTYCZNE
ATTITUDES OF POLISH PHYSICIANS TOWARDS EXTENDING COMPETENCIES OF NURSES AND MIDWIVES WITH RESPECT TO PRESCRIBING MEDICINES 270

Tetyana O. Kryuchko, Inna M. Nesina, Olha Ya.Tkachenko
DIAGNOSTIC ALGORITHM AND PECULIARITIES OF MONITORING FOR INFANTS WITH DISORDERS OF THE GASTROINTESTINAL TRACT
ALGORYTM DIAGNOSTYCZNY I ODMIENNOŚCI W MONITOROWANIU SCHORZEŃ UKŁADU ŻOŁĄDKOWO-JELITOWEGO U NIEMOWLĄT 275

Olena V. Solyeyko, Iryna P. Osypenko, Tetyana V. Galych, Mariya O. Chernykh
ASSESSMENT OF REHABILITATION POTENTIAL IN PATIENTS WITH VASCULAR DYSFUNCTION CAUSED BY UNDIFFERENTIATED CONNECTIVE TISSUE DYSPLASIA
OCENA POTENCJAŁU REHABILITACYJNEGO U CHORYCH Z DYSFUNKCJĄ NACZYNIOWĄ SPOWODOWANĄ NIEZRÓŻNICOWANĄ DYSPLAZJĄ TKANKI ŁĄCZNEJ 282

Nataliya I. Chekalina
RESVERATROL HAS A POSITIVE EFFECT ON PARAMETERS OF CENTRAL HEMODYNAMICS AND MYOCARDIAL ISCHEMIA IN PATIENTS WITH STABLE CORONARY HEART DISEASE
RESWERATROL CECHUJE SIĘ KORZYSTNYM WPŁYWEM NA PARAMETRY CENTRALNEGO UKŁADU KRĄŻENIA ORAZ STOPIEŃ NIEDOKRWIENIA MIOKARDIUM U PACJENTÓW ZE STABILNĄ CHOROBĄ NIEDOKRWIENNĄ SERCA 286

Валерий Г. Волков, Елена М. Гусева
К ВОПРОСУ О ПРОФИЛАКТИКЕ КРОВОТЕЧЕНИЯ В ПОСЛЕДОВОМ И РАННЕМ ПОСЛЕРОДОВОМ ПЕРИОДАХ
PREVENTION POSTPARTUM HEMORRHAGE 292

Maiia M. Ananieva, Mariia O. Faustova, Iaroslav O. Basarab, Galina A. Loban'
***KOCURIA ROSEA, KOCURIA KRISTINAE, LEUCONOSTOC MESENTEROIDES* AS CARIES-CAUSING REPRESENTATIVES OF ORAL MICROFLORA**
KOCURIA ROSEA, KOCURIA KRISTINAE ORAZ LEUCONOSTOC MESENTEROIDES JAKO PRZYKŁADY MIKROFLORY JAMY USTNEJ POWODUJĄCEJ PRÓCHNICĘ 296

Vladyslav Smiianov, Izabela Witczak, Olga Smiianova, Lesia Rudenko
MONITORING OF AWARENESS LEVEL IN DISPENSARY PATIENTS WITH ARTERIAL HYPERTENSION
MONITOROWANIE STOPNIA ŚWIADOMOŚCI U PACJENTÓW W OPIECE AMBULATORYJNEJ LECZONYCH Z POWODU NADCIŚNIENIA TĘTNICZEGO 299

Vyacheslav Zhdan, Galina Khaymenova, Lyudmila Shilkina, Daria Martynyuk, Marina Babanina, Tatyana Mamontova
DETERMINE THE EFFECTIVENESS OF LIPID-LOWERING THERAPY IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE COMBINED WITH CORONARY HEART DISEASE
OCENA SKUTECZNOŚCI TERAPII HIPOLIPEMIZUJĄCEJ U PACJENTÓW Z PRZEWLEKŁĄ OBTURACYJNĄ CHOROBĄ PŁUC I CHOROBĄ NIEDOKRWIENNĄ SERCA 303

DIAGNOSTIC ALGORITHM AND PECULIARITIES OF MONITORING FOR INFANTS WITH DISORDERS OF THE GASTROINTESTINAL TRACT

ALGORYTM DIAGNOSTYCZNY I ODMIENNOŚCI W MONITOROWANIU SCHORZEŃ UKŁADU ŻOŁĄDKOWO-JELITOWEGO U NIEMOWLĄT

Tetyana O. Kryuchko, Inna M. Nesina, Olha Ya.Tkachenko
HIGHER STATE EDUCATIONAL ESTABLISHMENT OF UKRAINE "UKRAINIAN MEDICAL STOMATOLOGICAL ACADEMY", POLTAVA, UKRAINE

ABSTRACT

Introduction: The most common medical conditions in infants, which belong to pediatric and gastroenterological disease areas, are functional gastrointestinal disorders, food hypersensitivity and food allergy. First of all, these symptoms can disguise lactase deficiency, cow's milk protein allergy, eosinophilic gastroenteritis, allergic proctocolitis, gastrointestinal manifestations of atopic dermatitis, functional disorders of gastrointestinal and biliary tract, etc.

The aim of our study was to develop an algorithm of monitoring for infants with disorders of the gastrointestinal tract and to study the efficacy of probiotic and enzyme replacement therapy.

Materials and metods: 47 children aged 1 to 3 years with gastrointestinal and atopic dermatitis symptoms underwent clinical and laboratory examinations.

Results: Analysis of additional examination revealed the causes of gastrointestinal disorders, and the following diagnoses were made: 15 children (32 %) had secondary lactase deficiency, 9 children (19 %) had sensitization to cow's milk protein and caseins. Molecular-genetic analysis of C > T polymorphism at position 13910 of lactase gene (LCT) demonstrated that C/C-13910 genotype was observed in 44.7 % of children, C/T-13910 heterozygous genotype was found in 36.2 %, and 19.1 % of children had T/T-13910 genotype; these were interpreted in conjunction with other clinical criteria for verification of secondary lactase deficiency diagnosis.

Conclusions: Assessment of children over time during their treatment showed that combined therapy using lactase preparation and probiotics contributed to relief of clinical symptoms. All patients had their fecal pH increased (> 5.5), whereas the majority of children demonstrated improvement yet on days 2–3 (i.e., decrease in pain syndrome, flatulency, and stool frequency; restoration of normal stool consistency).

Based on the obtained data, we proposed a practical algorithm for verification and monitoring of children with gastrointestinal disorders.

KEY WORDS: infants, functional gastrointestinal disorders, food allergy, lactase deficiency.

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INTRODUCTION

The globalization of the modern world, propagation of western models, values, institutions, and unlimited access to sources of information gave the unique possibilities to use clinical guidelines, developed by leading world experts, in everyday medical practice. Nowadays, the principles of high-quality clinical practice are essential for Ukraine, as they contribute to the implementation of medical care protocols into the national healthcare system.

Having analyzed the reasons for which parents of infants visit pediatricians, we identified common errors in symptom interpretation: fluid excrements or a tendency to constipations – as a sign of dysbacteriosis; excessive infant crying and irritability – as one of the symptoms of hunger or teething; rash on the body – as a food allergy. Besides, the views on providing medical care for such patients have changed many times over the past years in accordance with the public views on disease nature, level of scientific knowledge, available scientific evidence, degree of training and professional development.

The most common medical conditions in infants, which belong to pediatric and gastroenterological disease areas, are functional gastrointestinal disorders (FGID), food hypersensitivity and food allergy. FGID (infant regurgitation, rumination syndrome, intestinal colics, diarrhea, constipation, etc.) often progress with undiagnosed food intolerance. First of all, these symptoms can disguise lactase deficiency (LD), cow's milk protein allergy (CMPA), eosinophilic gastroenteritis, allergic proctocolitis, gastrointestinal manifestations of atopic dermatitis, functional disorders of gastrointestinal and biliary tract, etc. For example, epidemiological data show that CMPA manifests with gastrointestinal symptoms in 32–60 % of cases; with skin symptoms – in 4.5–90 %; with anaphylaxis – in 0.8–9 % of patients [1]. Topicality of the problem is caused by both insufficient knowledge of the various mechanisms

of how these symptoms occur and incorrect diagnosis and, therefore, ineffective treatment of these patients.

Today there is no doubt that the intestinal tract is not limited to digestive function; it is also an important immune organ [2, 3]. The cells of intestinal mucosa are involved in the process of food tolerance, preventing pathological immune reactions to food proteins. Impairment of cavitary and parietal digestion in the intestinal tract leads to destabilization of metabolism, formation of nutritional deficiency, multiple deficiency conditions, food intolerance (FI) [4, 5]. Formation of the intestinal barrier belongs to the most important factors that influence the development of allergic sensitization [6, 8]. Maturation of the digestive system is a critically important period, whereas a transfer from hemotrophic to lactotrophic feeding type occurs. Despite significant achievements in the study of food intolerance mechanisms in children and adults, the reasons of impaired intestinal absorption and food allergy formation are unknown so far.

The most common type of food intolerance in children is lactose intolerance (hypolactasia, lactase deficiency). Profound interest of pediatricians to the problem of LD is due to the fact that the main food for infants is represented by milk and dairy products. Up to 70 % of LD in children of this age is acquired (secondary), which is conditioned by a decrease in lactase activity associated with enterocyte disorder [7, 9]. Large-scale implementation of molecular genetic tests in clinical practice led to overdiagnosis of lactase deficiency in infants. Interpretation of genetic test results in commercial laboratories induced origination of unreasonable recommendations related to the stopping of breastfeeding and/or long-term feeding with lactose-free formulae. Genetic tests, in most scientists' opinion, are to diagnose enzyme deficiency in adult patients. As for children, genetic methods can be used as an explorative factor of a comprehensive study, given that lactase activity decreases with age, which is considered to be a genetically programmed autosomal recessive process. Adult type of lactase deficiency occurs more often after 3–5 years of life and is marked by increasing gastrointestinal symptoms with age. Secondary LD is characterized by decreased lactase activity due to enterocyte disorder, which occurs in infectious, allergic (including cow's milk protein allergy) or other inflammatory process in the intestinal tract, or atrophic changes of intestine mucosa. A quite controversial subject of studies is represented, on the one hand, by prebiotic capacity of lactose which prevents the development of intestinal inflammatory diseases, and, on the other hand, by galactose-induced senile cataract in people with lactase persistence or lactose intolerance in atherosclerosis, ovarian cancer, malaria [9, 10].

Parents' and children's complaints of an allergic reaction after cow's milk are much more common than a proven allergy to cow's milk protein (ranging 1 % to 17.5 % in children under 5 years; 1 % to 13.5 % in children of 5–16 years and 1 % to 4 % in adults) [2, 11]. Every third child with atopic dermatitis (AD) has an allergy to cow's milk protein which is confirmed by an elimination diet and a challenge test [2, 11, 12]. The role of non-IgE-mediated mechanisms in the formation of gastrointestinal manifestations of FA currently requires further study. In recent years, the effect of gastrointestinal microbiocenosis on the immune system development and food tolerance formation has been intensively studied. Various disorders in the composition of intestinal microflora are common in children with different manifestations of allergic diseases [8, 12, 13]. Also, some differences were observed between metabolic activity of intestinal microflora in children with and without atopy [13, 14, 18]. However, no algorithms for intestinal microbiota correction were developed so far for children with the symptoms of food intolerance and food allergy with regard to modern capabilities of dietary treatment.

THE AIM

The aim of our study was to develop an algorithm of monitoring for infants with disorders of the gastrointestinal tract and to study the efficacy of probiotic and enzyme replacement therapy.

MATERIALS AND METHODS

47 children aged 1 to 3 years with gastrointestinal and atopic dermatitis symptoms were examined. Observational period lasted for 6 months and included inpatient treatment course (an average of 10–14 days) and ambulatory monitoring with 4 visits to the Clinical Center. Before inclusion of patients into this research project, written informed consent was obtained from the parents. Patient selection to the groups under examination was carried out according to the criteria that formed the basis of the study design. During 3–4 weeks before hospitalization, children had gastrointestinal disorders and body rash; none of them demonstrated any effect after following outpatient recommendations on dietary correction.

Methods of examination: detailed analysis of life history and disease history; clinical index assessment for main symptoms; assessment of atopic dermatitis severity by means of SCORAD index; clinical blood analysis and urinalysis; biochemical blood analysis; eosinophil cationic protein test; bacteriological and coprological examination to determine pH and fecal excretion of carbohydrates; genetic test for lactose intolerance (risk assessment for different genotypes); allergic examination; determination of total and specific IgE in serum; abdominal cavity ultrasound. Clinical index was calculated by means of a 4-point score (0, 1, 2, 3 points) for the following eight symptoms: fluid excrements/constipations, bloating, colics, regurgitation, agitation after food, troubled sleep, poor appetite, poor weight gain.

Sensitization to cow's milk proteins was assessed by ImmunoCAP (kU/l). Sensibilization markers: cow's milk (f2), casein (f78). For the obtained results of genetic testing, the data on possible genotype variants were interpreted as follows: C/C genotype was associated with congenital LD of adult type; a child was homozygous for the allele that determined the lack of lactase persistence (a recessive trait); C/T genotype indicated a variable level of lactase deficiency due to genetic polymorphism; these individuals most often develop secondary LD; T/T genotype was indicative of little chance of this disease development (a dominant trait). Clinical diagnosis verification was carried out using the existing regulatory documents.

At the inpatient department, the children were prescribed elimination dietary treatment; if indicated – antihistamines, enzymatic agents, enterosorbents and medications for adjusting intestinal motility, topical preparations for skin application in dependence on the morphological characteristics of rash. As for infants who were breastfed, elimination diet was prescribed to their mothers, excluding obligate allergens and cow's milk. Formula-fed infants with intolerance to cow's milk were prescribed extensively hydrolyzed formula; children who were having general diet were fully or partially deprived of milk. In order to monitor the intensity of gastrointestinal and skin clinical manifestations we recommended keeping a diet diary.

In addition to the background therapy, children received Lacidokap probiotic containing live lyophilized lactic acid bacteria Lactobacillus rhamnosus R0011 and Lactobacillus acidophilus R0052, and Mamalak lactase enzyme (in drops and capsules) calculated as 750 U of lactase per 100 ml of milk [9, 16]. Medications were administered according to the product label.

Processing of numerical data was carried out by means of mathematical methods generally accepted in medical statistics. The mean values (M) and errors of the mean (m) of the studied parameters were calculated. Statistical significance was determined by Student's ttest.

RESULTS

Having analyzed the age peculiarities, it was found that first-year infants prevailed (68 %); infants of 1 to 2 years made up 17 %; of 2 years and over – 15 % with a tendency to male prevalence regardless of age. By analyzing disease history and clinical data it was established that the onset of atopic dermatitis occurred under 6 months of age in almost half of the studied children (46.8 %). It should also be noted that gastrointestinal disorders manifested first in the majority of these children. A detailed evaluation of medical history in children after 1 year of age revealed clear indications of allergic reactions related to food; the onset in most cases coincided with the introduction of feeding formulae into diet and was primarily characterized by occurrence of gastrointestinal disorders. In 34 % of cases the onset of allergy started with skin symptoms. A detailed evaluation of medical history revealed that in a third of cases, breastfeeding mothers had a plenty of milk-containing products.

Analysis of additional examination revealed the causes of gastrointestinal disorders, and the following diagnoses were made: 15 children (32 %) had secondary lactase deficiency, 9 children (19 %) had sensitization to cow's milk protein and caseins. Quantitative determination of sensitization level allowed to identify severity of cow's milk allergy and recommend a dietary correction.

Molecular-genetic analysis of C>T polymorphism at position 13910 of lactase gene (LCT) demonstrated that C/C-13910 genotype was observed in 44.7 % of children, C/T-13910 heterozygous genotype was found in 36.2 %, and 19.1% of children had T/T-13910 genotype; these were interpreted in conjunction with other clinical criteria for verification of secondary lactase deficiency diagnosis.

Gastrointestinal disorders are quite typical clinical manifestations of atopic dermatitis and food intolerance, and can be regarded as a local response to an orally taken allergen. Clinical symptoms in the studied children were represented by frequent watery, frothy stool, with a sour smell (72.3 %); bloating, intestinal colics and flatulence were recorded in more than 90 % of patients. More than half of children had frequent regurgitation. Syndromes with constipation and vomiting, by contrast, were rarely observed and diagnosed only in 14 % of patients.

Coprological examination demonstrated maldigestion signs in all patients, in particular: mixed steatorrhea – 46.8 % of children, amylorrhea – 89.36 %, creatorrhoea – 31.91 %, digested fiber in the faeces – 55.3 %, iodophilic flora – 72.34 % of children; fecal pH – 5.27 ± 0.31. When studying fecal excretion of carbohydrates, we observed age-dependent trend in the examined children: increased excretion of lactose in early infants was observed in 75 % versus 33.3 % of cases in children older than 1 year, including all patients with sensibilization to cow's milk protein, which probably reflects the severity of enterocyte damage.

Abdominal cavity ultrasound showed that the majority of patients (80.9 %) had their pancreas changed in size and/or structure, in particular: enlargement was found in 17 children; increased echogenicity and/or pancreatic parenchyma inhomogeneity with hyperechoic inclusions – in 9 children; 29 children (61.7 %) presented with the signs of the biliary dysfunction. Diagnosed disorders lead to cavitary digestion impairment, and accumulation of incompletely broken macromolecules in the intestinal lumen promotes sensitization.

Age-dependent analysis of intestinal microbiota in the studied children demonstrated that 1-year-old patients more often had II, III, and IV degree dysbiosis than the children after one year (86.8 % vs. 33.3 %, ($p < 0.05$), most common were *S.aureus* – more than 10^5 ufc/g and *Candida* – more than 10^4 ufc/g. Typical symptoms of intestinal dysbiosis were: reduction in the content of bifidobacterium flora (68 %), lactobacilli (57.5 %), Escherichia coli (74.5 %); the presence of Staphylococcus aureus (34 %) and opportunistic bacteria (Klebsiella (21.3 %), Proteus (12.8 %), Citrobacter (19.2 %), yeast-like fungi (29.8 %).

Assessment of children over time during their treatment showed that combined therapy using lactase preparation and probiotics contributed to relief of clinical symptoms, in particular to a rapid decrease of abnormal signs (fluid excrements, colics, skin rash). All patients had their fecal pH increased (> 5.5), whereas the majority of children demonstrated improvement yet on days 2–3 (i.e., decrease in pain syndrome, flatulency, and stool frequency; restoration of normal stool consistency). Thus, intestinal colics on day 7 remained only in a third of children; 35 % of patients still suffered from abdominal pain and 40 % of patients kept reporting unstable stool (Figure 1).

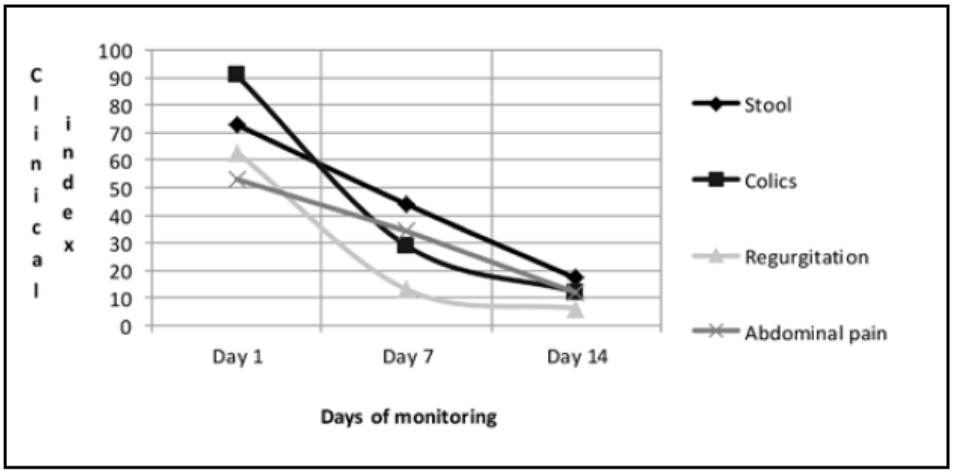

Fig. 1. Clinical Index Profile for Gastrointestinal Manifestations

Table I. Eosinophil Cationic Protein Profile in the Course of Treatment

	Children with FGID	Children with FGID + LD	Children with FGID + Cow's Milk Protein Allergy
Pre-Treatment	48.2 (39.4–56.1)	44.6 (38.8–59.2)	51.6 (38.2–63.4)
Post-Treatment	24.4 (19.6–26.4) *	22.8 (18.9–24.5) *	29.7 (24.2–32.3) *

** – p <0.05 in pre-treatment vs. post-treatment.*

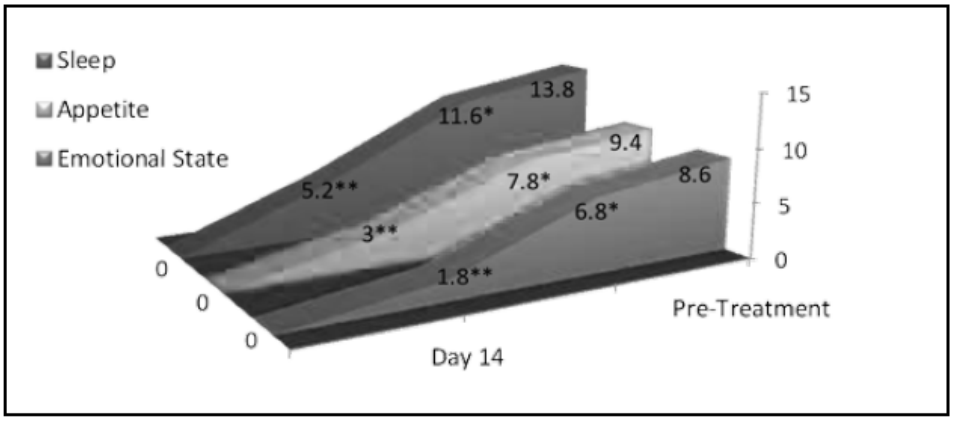

Fig. 2. Subjective symptoms progression in the course of treatment

The disorders revealed in a stool test resolved by day 14 of treatment. After the treatment, only 8 (17 %) patients had the stool frequency and consistency that required additional probiotics course. In the children after one year, we observed a tendency to normalization of bifidobacteria and E. coli content, but the number of children with high level of *S.aureus* increased (42.6 %). One should not rule out that in the setting of microflora improvement, high levels of Staphylococcus aureus are one of the factors contributing to the chronic course of atopic dermatitis.

Severity of atopic dermatitis symptoms was assessed by SCORAD index during the study. Mild symptoms were observed in 5 (31.9 %) patients, moderate – in 21 (44.7 %), and severe – in 11 (23.4 %) children. When monitoring the score dynamics during the treatment, we established that regression of skin manifestations clearly depended on the isolation of FGID symptoms or presence of comorbidity. The mean SCORAD score did not significantly differ among children at the baseline, but on assessment days 7 and 14 the patients with intolerance to cow's milk protein presented with significantly higher levels, which is primarily due to a more severe course of disease induced by food intolerance, especially IgE-dependent forms.

In order to assess the severity of allergic reactions, eosinophilic cationic protein (ECP) was measured (Table 1).

These data suggest that the level of ECP (one of the most toxic proteins in eosinophilic granules) significantly decreases in the course of treatment in all children and clearly correlates with the activity of allergic inflammation ($p < 0.05$), which is primarily characterized by eosinophil infiltration of tissues. Cytokine cascade of allergic reaction markers, in particular ECP, remains in a dynamic state, and its concentrations and effects on the immune response change in dependence on the disease phase (exacerbation or remission).

The study demonstrated good tolerability of substitution treatment and probiotic therapy in the examined patients. All the children presented with the improvement of appetite, sleep, and emotional state after the treatment (Figure 2).

DISCUSSION

In the course of evaluation of medical history data, we analyzed the factors of atopy realization and found out that allergy to cow's milk, eggs, cereals often has its onset during the first year of life; intolerance to fish, some vegetables, fruits, legumes and nuts occurs by 2–3 years of age; and after three years of age, sensitization to aeroallergens (pollen, domestic allergens) usually develops, with cross-reactions occurring between them. The obtained results regarding age peculiarities of food intolerance formation in children clearly correlate with the data from other researchers [11]. At present, it is clearly stated that food sensitization often acts as a trigger and can develop from the first days or months of life. Further, age-related evolution is observed: 24 % of children who were timely and adequately cured and given prevention measures end up with a clinical recovery; in 46 % of children there is a transformation of food allergy clinical manifestations with target organ change-over ("atopic march") and the formation of hypersensitivity to other types of allergens. Gastrointestinal manifestations, which play an important role in realization of allergy clinical symptoms, often manifest first, before the occurrence of skin rash, and imitate other diseases. In fact, a specific food product which causes gastrointestinal symptoms is detected in 67 % of children with allergic diseases [12].

To assess the dynamics of clinical manifestations and overall severity of atopic dermatitis, we used SCORAD scale. Children with allergy to cow's milk had a bit slower symptom resolution, which was caused by the severity of disease realized as a generally IgE-mediated allergic manifestation of atopic predisposition. In the patients with IgE-independent allergy the latter is represented mainly by gastrointestinal disorders (guidelines DRACMA, WAO, 2010). Unlike asthma and rhinitis, there are no reliable epidemiological studies on the prevalence of food allergy. Epidemiological data are considered reliable, if the diagnosis of allergy to cow's milk was confirmed by provocative tests [1]. B-lactoglobulin was earlier considered to be one of the most important cow's milk allergens, because it is absent in breast milk. But the recent studies proved the important role of other proteins, including casein (Bos d 8), in the etiology of allergic diseases. Most often patients are sensitized to alpha (100 %) and kappa (91.7 %) caseins.

In pediatric practice, the information regarding cross-reactivity of milk from different mammals is very important. The greatest homology is observed among the proteins of cow's, sheep's and goat's milk (Bovidae family of ruminant mammals). It should also be remembered that milk preserves its allergenic activity after heating and boiling, which was clinically proved, since milk boiling for 10 minutes reduces reaction in the patients who respond only to bovine serum albumin and beta-lactoglobulin, but the reaction to caseins remains unchanged [1].

There are objective markers of allergic inflammation, the level of which determines the degree of affection of any system. These markers include eosinophilia, increased levels of eosinophilic cationic protein, tryptase, leukotrienes and other mediators of inflammation. Eosinophilic cationic protein is an objective marker of eosinophil activation. It constitutes more than 70 % of all proteins which produce eosinophils, stimulates mucus secretion, inhibits T-lymphocyte proliferation, is cytotoxic and affects blood clotting. Comparing this parameter over time in the setting of treatment, we have established a positive trend to its decrease, which indicated the effectiveness and reasonability of the proposed therapeutic scheme.

Currently, there are several phenotypes of lactose metabolism: lactase persistence, characterized by preserving of high activity of lactase enzyme in adulthood; hypolactasia, or LD, which may be caused by physiological age-related decrease in lactase activity or lactase deficiency due to different pathological processes in the digestive tract; malabsorption of lactose, which is based on the ineffectiveness of absorption; lactose maldigestion caused by impaired lactose fermentation; lactose intolerance [15, 16, 17].

Analysis of the peculiarities of intestinal microflora composition in children with gastrointestinal disorders showed that bifidobacteria lack was observed equally often regardless of clinical manifestations, and defects of aerobic component of microflora depended on the severity of allergic process and sensitization features. Thus, gastrointestinal manifestations in children with allergy to cow's milk protein was accompanied by a more significant increase in content of microflora aerobic component, the associations of potentially pathogenic microflora (PPM), S. aureus of more than 105 ufc/g; severity of skin manifestations of allergy was combined with more frequent dominance of coccal microflora ($p < 0.01$), detection of PPM with aggressive potential (haemolyzing forms of E. coli, haemolyzing enterococcus), S. aureus, Candida fungi, PPM associations ($p < 0.05$). Scientific works accentuate the pathogenic role of microflora disorders in the formation of allergic diseases. Forno (2008) in his study showed that reduced variety of intestinal microflora for up to one month served as a risk factor for atopy for one year (Shannon Index). Thus, oral use of

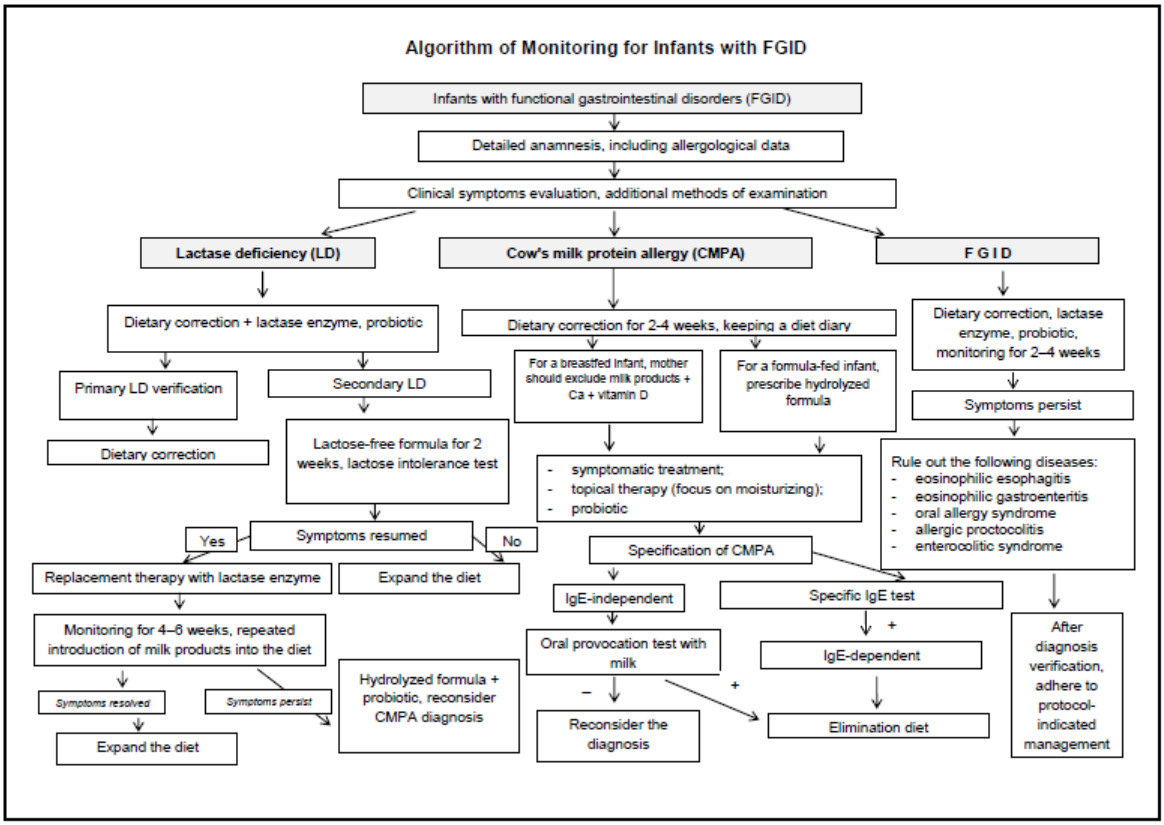

Fig. 3. Algorithm of Monitoring for Infants with FGID

combination probiotics reduces symptoms of dermatitis, with a decrease of serum eosinophilic cationic protein level. Results of clinical studies indicate that probiotics promote regression of inflammatory reaction symptoms in allergic diseases outside the gastrointestinal environment. Thus, a combination of enzyme-replacement therapy and probiotic bacteria for allergic disease treatment has demonstrated promising results at present, though it requires further studies and generalization.

Great importance in the formation of tolerance belongs to anatomical and functional capacity of epithelial barrier of intestinal mucosa. This is directly related to proper immune system functioning associated with gastrointestinal mucous membranes (GALT – gut-associated lymphoid tissue), which are responsible for good innate and adaptive immune responses. Examination of clinical manifestations of food allergy in children with atopic dermatitis revealed that skin is also an immune organ, where the immune response is initiated in the skin-associated lymphoid tissues (SALT). Dendritic skin cells recognize and capture antigens; then the cascade of immune responses sets in motion, which implements the immune response manifested through clinical symptoms of AD.

It should also be remembered that 50–90 % of clinical manifestations of hypersensitivity to food allergens are due to IgE-independent mechanisms of development rather than immune mechanisms, as was a common misconception among many doctors. Therefore, evaluation of physical data should be combined with anamnestic and laboratory data and, ideally, correlate with oral provocation test, which remains the gold standard in food allergy diagnosis [17, 19].

CONCLUSION

Balanced approach to diagnosis is a key factor for proper selection of further management in children with FGID, because monitoring and prognosis in transient lactase deficiency, intolerance to cow's milk protein, anaphylaxis, eosinophilic esophagitis, or atopic dermatitis are radically different. By organizing the data, we can offer a practical algorithm that helps not only to verify the diagnosis, but also to observe diligently this category of children and refer them to a further level of medical care, if necessary (Figure. 3.).

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ADDRESS FOR CORRESPONDENCE

Inna M. Nesina
Department of Pediatrics №2
State Higher Education Institution of Ukraine
"Ukrainian Medical Stomatological Academy"
34 Shevchenka str., 36000 Poltava, Ukraine
tel.: +38(050)6004708
e-mail.: nesinainna@gmail.com

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