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State of intestinal microflora in children with atopic dermatitis and role of probiotics in its correction

Keywords: *atopic dermatitis, intestinal microflora, probiotics, children.*

Atopic dermatitis is a chronic allergic disease which is progressing in people with genetic predisposition to atopy and is specified by recrudescent disease course, age peculiarities of clinical signs, exudative and/or lichenoid rash, increase in serum immunoglobulin E and specific (allergenic) and nonspecific hypersensitivity. Atopic dermatitis is a serious medical problem which is faced by the doctors of different specialties in their practice. It is determined by wide prevalence rate in paediatric population. Lately, many countries of the world are distinguished by high tendency to children's atopic dermatitis (AD) quantity increase and its more severe progression, which brings life restriction and social disadaptation. The prevalence of AD among the megapolis inhabitants makes about 15 % and above [3, 4, 17, 32].

The necessary diagnostic criteria of atopic dermatitis are as follows: skin cover itch, typical skin rush morphology and location (in children); eczematoid skin rush, located on the face and extensive limb surface; in adults – lichenification and excoriation on flexor limb surface; recrudescent disease course, atopy in anamnesis or genetic predisposition to atopy [4, 12].

Additional criteria: xerosis (skin dryness); palmar ichthyosis, immediate reaction for skin testing with allergen; location of dermatic process on the wrists and feet; nipple eczema; susceptibility to infectious skin diseases, connected with cellular immunity disorder, the beginning of the disease in the early childhood; erythrodermatitis, recrudescent conjunctivitis; Dennie-Morgan fold (infraorbital fold); keratoconus (conic corneal outpouching); the front subcapsular cataract; high IgE in the blood serum [11, 12, 29].

The functional state of digestive tract plays a significant role in AD process. The surface of the small bowel has contacts with the external foreign substance ten times more than inspiratory epithelium and 300 times more than skin surface. In physiological terms of digestion system there are anatomical, physiological and immunological barriers which prevent from food antigen penetration into internal environment of the body. Considering the age anatomical and physiological characteristics of digestion, the mentioned barriers failure occurs in childhood. The digestion barrier damage as a result of inflammatory, infectious and parasitic diseases potentiates food sensibilization [5, 8, 22].

One of the hypotheses of forming AD is a hygienic or «the hypothesis of microorganism deprivation» which has been the subject of discussion since 1989, when the British professor of epidemiology David P. Strachan published the article «Hay fever, hygiene, and household size» [32]. Microorganisms, colonizing the bowel in early postnatal period take part in the activation of genetic and adaptive immunity, bacteria necessary for successful maturation of GALT – gut associated lymphoid tissue. Microbe exposition in early lifetime provides the activation of Treg and dendritic cells and correlates with less allergy disease rate. Decrease of bacterium antigenes contact (provided with family size decrease, plannable vaccination, wide use of antibiotics, assanation) prevents from switching of polarized Th2 immune response, formed in prenatal and neonatal life period to Th1 cellar immune response [18, 19, 25].

«The hypothesis of microbiota» accompanies the hygienic one. The concept claims that qualitative and quantitative defects of intestinal microflora as a result of wide use of antibiotics, change of diet generally caused the change in qualitative composition of intestinal microflora and disorder in forming process of oral immunological tolerance. Incomplete or inappropriate microbe stimulation cause the

reduction of bowels surface, change in ferment patterns of mucous of intestinal barrier, IgA decrease. As a result, disbalance of intestinal microflora contributes to persistence of Th2-oriented immune response.

The epidemiological and clinic data, supporting «The hypothesis of microbiota» are as follows: 1) positive correlative interrelation between risk of asthma /allergy emergence and usage of antibiotics in developed European countries, 2) accurate connection between change in fecal microbiota and atopy, 3) effect of probiotics and diet recommendation in prevention and treatment of allergy [6, 23, 29].

Protective intestinal microflora, presented by lactobacteria, bifidobacteria and collibacillus with normal ferment characteristics provide microbiota uniformity due to colony resistance. Thus, bifidobacteria, lactobacteria expose lactic and acetic acid, other substances having selective antimicrobic action. Acid environment provided by life activity of these microorganisms prevent from penetration and fastening of the pathologic microbes, which are uncharacteristic of the given biotope to the mucosa. Moreover, bifidobacteria stimulate cellar component of immune system and take part in immunoglobulin synthesis. The mentioned bacteria play the role of natural biosorbent and are able to cumulate a big number of heavy metal, carbolic acid, formaldehyde and other toxic substances. Lactobacteria to a large extent reduce allergen absorbing in the intestine and stimulate the synthesis of immunoglobulin A, which prevent from admission and absorption of food allergens especially in early childhood [3, 8].Subpopulation of regulatory lymphocytes, inducing by Lactobacillus rhamnosus, synthesizes tumor growth factor – TGF–β, preventing from atopy development and anti-inflammatory IL10, which switches differentiation from Th2 to Th1 – immune response [13, 19].

Considering all mentioned above, it is appropriate to study quantitative and qualitative composition of intestinal microflora in children with AD, interrelation of allergy and dysbacteriosis. Disorder in colonization resistance of intestine, connected with change in composition of resident microflora, causes colonization of pathogenic and opportunistic bacteria, basic dysfunction, which result in dysbacteriosis emergence. Besides, intestinal dysbacteriosis might be primary and precedes allergy emergence or post primary and be caused by its gastrointestinal signs [1, 25, 31].

The results of experimental research about the influence of western high-carbon and high-fat diet pattern on the composition of intestinal biocoenosis appear to be interesting. The mice were nourished by low-fat plant food. After contamination of human microflora of a host on western diet, increased quantity of Clostridium innocuum, Eubacterium dolichum, Catenibacterium mitsuokai and Enterococcus spp. was detected parallel to the reduce of Bacteroides spp. concentration [13].

Intestinal dysbiosis is a clinical syndrome that results from some diseases and clinical situations and is characterized by the symptoms of enteropathy, by the changes in qualitative and quantitative composition of normal microbiotia, as well as by the translocation of its different types into alien biotopes and their overgrowth [2].

The underlying causes of intestinal dysbiosis is retarded breast-feeding, child's irrational nutrition, functional gastrointestinal tract disorders, gastrointestinal tract diseases, particularly those related to the malabsorbtion syndrome (lactase deficiency, coeliac disease, cystic fibrosis and others), antibiotic treatment (especially in the first days of life) [3, 31].

Kalliomäki M. and co-authors (2001), Brown K. (2012) illustrated that the proportion of Bifidobacterium and Clostridium spp. in the intestinal of children with AD is lower due to the low colonization of bifidobacterium and the overgrowth of *C difficile* and *E coli* [14, 19]. The high concentration of the latter reduces the activation of Treg cells and increases the permeability of intestinal wall for allergens and toxins. Children who do not have a clinical manifestation of allergy possess a higher concentration of Bifidobacterium by the age of two, than patients with AD. The intestine of children with food allergy manifests the overgrowth of Staphilococcus aureus, E. coli with modified properties, fungi Candida, that promote autosensibilization of the organism provoking immune allergic reactions, mainly IgE-type [8, 13, 21].

Numerous experimental data related to particularities of the intestinal biocoenosis composition of children with AD and its impact on the formation of the immune response formed the basis of the study of preventive and therapeutic efficiency of probiotics for children with allergy [10, 30].

In 1908 Russian immunologist Illia Mechnikov discovered that lactobacillus, contained in fermented milk are good for human health. This discovery provided the basis for further research concerning potential positive impacts of probiotics. The Food and Drug Organization of the United Nations (FAO) and the World Health Organization (WHO) gave the following definition to probiotics: «living microorganisms that carry a positive impact on organism, when used in corresponding doses» [1, 18, 25].

Modern probiotics have to meet the following criteria: contain microorganisms the probiotic effect of which is proved in randomized controlled studies; have stable clinical efficiency; be subject with phenotypic and genotypic classification; remain live; be non-pathogenic and non-toxic; do not provoke side-effects in case of long-term treatment; make positive effect on the organism (for example increase resistance to infections); have colonization potential, that is remain in the gastro-intestinal tract until the reach of a maximum positive result (be resistant to high acidity, organic and bile acids, anti-microbic toxins and ferments which are produced by pathogenic microbiotia); be stable and preserve vital bacteria during the extended conservation period [1, 2, 9, 18].

Probiotics make a three-level effect in the gastrointestinal tract. Non-immunologic effects of probiotics consist in concurrence with pathogenic bacteria for nutrients; changes in local pH, in-production of bacteriocins that suppress the development of pathogenic microorganisms; inactivation of superoxide radicals; stimulation of epithelial mucin production; reinforcement of intestinal barrier

Table 1.

Results of randomized placebo-controlled research of probiotics efficiency for the prevention and treatment of infant allergy

Author, year, number of patients	Probiotic strains	Administration scheme	Efficiency
KalliomakiM. etal. (2001, 2007, 2009) Mother-child, (n = 132)	*L. rhamnosus (LGG)*	2-4 weeks before delivery, then for children under the age of 6 months	↓ of AD cases, does not influence the SCORAD
Weston S. Et al. (2005) Children under the age of 6-18 months, (n = 56)	*L. fermentum*	During 8 weeks	↓ SCORAD (symptoms intensity and extention
BrowerM.L. (2006) Children under the age of 5 months, (n = 34)	*L. rhamnosus*	During 3 months	Absent
Kopp M.V. et al (2008) Mother-child, (n = 105)	*LGG*	4-6 weeks before delivery, then for children under the age of 6 months	Nor preventive, nor therapeutic effect
AbrahamssonT.L. etal. (2008) Mother-child, (n = 232)	*L. reuteri*	Since 36 gestation weeks, then for children under the age of 6 months	↓ IgE-associated AD, ↓ children of mothers with atopics – sensibilization
HuurreA. (2008) Mother-child, n = 171	*LGG+ B. lactis*	From the I trimester of pregnancy to the end of breast-feeding period	↑ TGF-β2 Mothers – protective effect in AD development
SohS.E. etal. (2008) Children under the age of 6 months, (n = 253)	*LGG+ B. longum*	During 6 months	Absent
Taylor A.L. (2007) Children under the age of 6 months (n = 231)	*L. acidophilus*	During 6 months	Absent
Gruber C. Et al. (2007) Children aged 3-12 months, (n = 102)	*L.rhamnosus*	During 9 months	Absent
Wickens 2008 / New Zealand (n = 471)	*Lactobacillus rhamnosus(HN001) or Bifidobacteriumanimalis ssp. lactis (HN019) /*	5 weeks before delivery children till 2 year	↓ of AD cases (L. rhamnosus) ↓ of severity (SCORAD ≥ 10) (L. rhamnosus) Does not influence the AD cases (B. lactis) ↑ Lactobacillus и Bifidobacterium in the intestinal
WestNP2009 (n = 180) Children aged 4-13 months	*Lactobacillus F-19*	Prenatally and 8 weeks after delivery	↓ of AD cases Increased Th1/Th2 index
Герасимов С.В. (2010) (n = 180), Children of the age of 1-3	*L. acidophilusDDS-1, B. Lactis UABLA-12,and fructooligosaccharide*	8 weeks	↓ SCORAD, CD4, CD25-lymphocytes, ↑ CD8

function by strengthening intercellular junctions; competitive inhibition of pathogen adhesion; mucin production; pathogenic toxins modification. Thus, Lactobacillus rhamnosus GG (LGG) и L. Casei reduce the concentration of Clostridia and multiply the concentration of bifidobacterium in the intestinal of infants with food allergy. Therefore the first two effect levels of probiotics are activated: in the intestinal lumen and wall [9, 18].

Immunological effects of probiotics consist in modulation of the function of macrophages laminapropria, secretory immunoglobulin A production, modulation of cytokine profile (TNF-β, IFNγ, IL-12, IL-4, IL-10), that are realized on a molecular level via Toll-like receptors (TLRs). Intestinal epithelial cells synthesize a big number of pattern-recognition receptors for recognition of mycobacteria – pathogen-associated molecular patterns (PAMPs).

One of the classes of these receptors – toll-like receptors (TLRs), the stimulation of which by certain PAMPs increases the production of Th1 cytokines (namely IL-10, TGF-β), as well as increases the synthesis of IgA in gut mucous wall. That is why probiotics can hold the newborn's Th1/Th2 balance in the absence of natural microbial impact. In particular, the analysis of peripheral mononuclear cells of children who took probiotic, showed a higher proportion of IFN-γ/IL-4 [9, 10, 17, 30, 32].

In 2013 Pillar Ingrid and co-authors held a survey of 187 scientific studies using research keywords «atopic dermatitis», «probiotics» in data bases of Medline, Lilacs Pub Med, selected 12 randomized double-blinded placebo controlled studies for the analysis of probiotics influence on children with AD and basic allergens allergy: cow's milk protein, egg, wheat/gliadine, codfish, peanut [24]. The following probiotic strains were used in studies: Lactobacillus rhamnosus GG, Lactobacillus rhamnosus, Lactobacillus GG, Lactobacillus fermentum VRI-033 PCC, Lactobacillus acidophilus NCFM, mixture of Lactobacillus rhamnosus GG, Lactobacillus LC 705 rhamnosus, Bifidobacterium breve Bbi 99 и Propioni bacterium freudenreichii SSPJS, as well as Bifidobacterium lactis Bb12 и Bifidobacterium lactis Bi-07 [15, 16]. The probiotics treatment duration varied from 4 to 12 weeks. Clinical efficiency and reduction of SCORAD index were taken as a primary endpoint. In general the treatment order of probiotics make a positive effect in almost 80 % of cases, furthermore the antenatal probiotics intake is more effective than postnatal. It was noticed that Lactobacillus probiotic stains do not usually make any effect on children with cow's milk protein allergy, which is connected with the fact that these bacteria need cow's milk protein for their growth. In addition, the Koppetal study (2008) and some other prospective studies established a connection between the intake of probiotics and the onset of asthma symptoms within 2 years of the follow-up period. That is why they emphasize that the choice of probiotics has to be species- and strain-specified, include a long period of follow-up monitoring [10, 28, 29].

Summary data related to the study of probiotics in the context of AD is presented in the table 1 [16, 25, 26, 27, 29].

Randomized placebo-controlled research Ecologic PandA, held in the Netherlands, the objective of which is the study of the role of pre- and postnatal probiotic bacterium intake in primary allergic diseases prevention, deserves particular attention. The combination of probiotic strains was selected on the basis of their *invitro* cytokine production. The mixture of probiotic strains included *B. bifidum W23, B. lactis W52 u Lc. Lactis W58 (Ecologic® Panda)* and was taken by pregnant women in the last 6 weeks of pregnancy and by their children during the first year of their lives.

The mixture of the designated probiotics reduced the risk of AD symptoms for 3-moths old children. The children who took probiotics showed early intestinal colonization by *Lc. lactis* and *Bifidobacterium spp.,* as well as showed a lower concentration of IL-5 ($p < 0,05$). The two-threefold concentration of IL-13 was discovered among children who did not take probiotics and had clinical AD signs by the age of 3 months [1, 20].

A combination of probiotics specially developed for pregnant women and young children and based on the results of the above-mentioned study have recently appeared at the pharmacological market of Ukraine: Ecologic PANDA (Fabricator: Winclove Bio Industries Laboratory, The Netherlands), that contains unless 1,0x109 CFU/g Bifidobacterium bifidum, Bifidobacterium lactis, Lactococcus lactis in 1 sachet. The drug «Lactomun» quickly restores the intestinal microflora and eliminates dysbacteriosis, reduces the allergy development risk, fortifies the immunity. It is stated that the studied strains activate the production of IL-10, suppressing the synthesis of proallergic cytokines IL-5 and IL-13.

Conclusion

In spite of a relatively big amount of studies dedicated to preventive probiotics efficiency for pregnant women from the risk-group and their clinical efficiency for young children's cutaneous symptoms of food allergy, the further studies are necessary for the specification of optimal strains, medicament doses, duration of treatment, as well as for the validization of the previous studies on the basis of a long-term (minimum 2 years) prospective monitoring of children who take probiotics. During the randomized research Ecologic PandA the choice of probiotic strains was based on *in vitro* data that concerns the inhibition of pro-allergic cytokines inhibition. The research showed preventive and therapeutic effects of *Bifidobacterium bifidum, Bifidobacterium lactis, Lactococcus lactis* combination that makes possible to prescribe «Lactomun» to young children having cutaneous allergy symptoms, to children from allergy risk-group as well as to pregnant women with burdened allergological anamnesis.

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