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Evaluation of the effectiveness of mineral correction in children with varying degrees of control of asthma

L. Ya. Litvinets [1]*

1. Ivano-Frankivsk State National Medical University, Ivano-Frankivsk, Ukraine
[Email: doclitvinetsl@gmail.com]

This paper presents the results of the evaluation bioelemental status in children with varying degrees of control of asthma. We conducted a complete physical examination of 107 children with asthma who were hospitalized in the Department of Allergic regional children's hospital in Ivano-Frankivsk and analyzed the features of their state of micro-and makroelemental provide. Thus, zinc content of children with uncontrolled asthma, comprising (0,52±0,02) mg%, was the lowest , with which is associated the decrease in antioxidant defense of enzyme systems and distortions of adequate response of the body to the action of allergens. Determination of copper in the blood of children with asthma, revealed the presence of severe hypercupremia of all the patients with bronchial asthma. Analysis of the survey results of the concentration of magnesium in the blood of children with asthma found that the content of bioelements in all the examined children was significantly reduced in relation to the comparison group. We observed the increasing of calcium levels in all the patients with asthma compared with healthy (P N<0.05), and the most clearly observed changes were fixed in children with uncontrolled asthma. Improved therapy (on the background of the basic application of Beres Drops Plus) substantially affected the blood levels of copper and zinc, while traditional was inefficient for correction of these blood bioelements, which correlated with the dynamics of clinical symptoms. This study helps to clarify the new and deepen the knowledge of the pathogenesis of asthma from the new positions, to broaden the possibilities to improve its diagnosis and treatment.

Keyword: Asthma, children, essential elements Beres Drops Plus.

1. Introduction

At present, there is no doubt the fact of the relationship of certain multifactorial diseases with the deficiency, excess or imbalance of macro (MaE) and microelements (ME) in the body [1, 3, 9, 15]. This is due primarily to the fact that the chemical elements are active centers of practically all the enzymes, hormones, antibodies, etc., it means that they influence a large number of vital processes [2, 4, 6, 8, 12].

The particular importance of dyselementosis acquire in childhood , due to the rapid growth and development of the body and a considerable intensity of metabolism, maturation of the immune and endocrine systems, which are primarily controlled by the body's response to the impact of environmental factors and the increased need for macro- and micronutrients [2, 9].

Particular attention in this regard should be paid to the pathology of allergy, including bronchial asthma (BA). Because in these patients from the food are excluded the obligate and cause valuable allergens commonly found in fruits, vegetables , fish, milk and so on. Under such circumstances, it may develop exogenous dyselementosis, which manifestations superimposed on the clinic of the main disease, and often exacerbate it.

Considering the asthma control as adequacy of its management, we can assume that the main goal of treatment is aimed at preventing and

eliminating of clinical symptoms and reduce further doses of corticosteroids. Traditional tactics of examination and appointment of health care measures in asthma does not provide diagnosis and correction of changes of MaE and ME status, which could reduce the effectiveness of the treatment of children and promote chronic disease process. After all, today we know that even subnormal supply of ME may result in lengthening the period of recovery and an increase in the frequency of exacerbations of chronic diseases [12].

All the information above was a prerequisite for the study.

The aim of our work was to study the characteristics of the MaE and ME status in patients with asthma, depending on the severity of the course and assess of the feasibility of correcting the detected changes.

2. Materials and methods

A comprehensive survey of 107 school children suffering from asthma was made. The diagnosis is verified by the Protocol of diagnosis and treatment of asthma in children (№ 767 from 27.12.2005). At the first stage of the study the results of the use of asthma control test (GINA, 2011) on the level of control the children with asthma were distributed as follows: the first group included 26 children (14 boys and 12 girls) with a mean age of (7,6±0,6) years with uncontrolled bronchial asthma course (UCBA). The second group formed 47 children (25 boys and 22 girls) with a mean age of (9, 1 ± 0, 7) years with partly controlled bronchial asthma (PCBA). The third group consisted of 34 children (16 boys and 18 girls) with a controlled flow of bronchial asthma (CBA). The mean age of patients of the third group was (11, 2 ± 0, 4) years.

Spending determination of Ca, Mg, Cu, Zn, Mn, Co (mg %) in peripheral blood erythrocytes by atomic absorption spectrophotometry [Babenko, G.O., 1996].

In order to explore the possibility of correction of changes in the state of essential elements the children of each group were divided into two groups: A - were treated for asthma control according to Protocol, B - combined protocol for the treatment of asthma control with using Beres Drops Plus (BDP) production of JSC "Beres Pharma" (Hungary, certificate of state registration № UA/9101/01/01 of 11.11. 2013). Subgroup A comprised 12 children with UCBA, 23 children with PCBA and 18 patients with CBA. Subgroup B - 14 children with UCBA, 24 children with PCBA and 16 with CBA. BDP were used in the following way: 2 courses for 28 days with an interval between for 2 months. Dosage of BDP is dependent on body weight: patients weighing 20-40 kg - 20 drops 2 times a day, with a body weight over 40 kg - 20 drops 3 times a day. The comparative analysis of biometals was made twice: before treatment with the inclusion in its complex BDP and after treatment (in 4-5 months). The control group was made up of 12 children of similar age.

All patients were examined after getting the informative consent of a child and his parents in accordance with GCP IHC.

Descriptive statistics for quantitative indicators are presented as absolute and relative values, standard deviation, midvalue and number of observations. For quality of indicators were used the percentages and the probability determined by comparing the shares. Statistical analysis of the results of research was carried out by using a standard computer program Microsoft Excel 5.0 and Statistica 5, 0.

3. Results

To assess the pathogenetic significance of MaE and ME in asthma of varying degrees of control we conducted to determine their content. We established a significant imbalance of micro-and macronutrients in erythrocytes of children suffering from asthma, and defined a clear dependence of the degree of control of the disease (Table 1).

Thus , determination of zinc level in erythrocytes showed that in general children with asthma observed significant reduction of this microelement (PN < 0.001) , the extent of which was partly determined by the control over the disease. However, in children with UCBA zinc content, comprising (0,52 ± 0,02) mg%, was the

lowest and differed significantly from that seen in healthy children and children with a higher degree of controllability of disease (P < 0.001).

Table 1: The level of macro- and microelements in the erythrocytes of the peripheral blood of healthy children and children with asthma (M±m)

Показник	**Healthy [1] (n=12)**	**UCBA [2] (n=26)**	**PCBA [3] (n=47)**	**CBA [4] (n=34)**
Ca, мг%	1,21±0,42	3,95±0,47 p_{1-2}<0,05	1,89±0,59 p_{2-3}<0,05	1,94±0,44 p_{2-4}<0,05
Mg, мг%	6,07±0,03	4,06±0,06 p_{1-2}<0,05	4,10±0,15 p_{1-3}<0,05	5,06±0,04 p_{1-4}<0,05
Cu, мг%	0,48±0,05	0,91±0,03 p_{1-2}<0,001	0,61±0,02 p_{1-3}<0,02 p_{2-3}<0,001	0,46±0,03 p_{2-4}<0,001 p_{3-4}<0,05
Zn, мг%	2,70±0,12	0,52±0,02 p_{1-2}<0,001	0,83±0,02 p_{1-3}<0,001	1,69±0,08 p_{1-4}<0,05 p_{2-4}<0,001 p_{3-4}<0,001
Mn, мг%	0,039±0,005	0,052±0,005	0,047±0,005	0,051±0,004
Co, мг%	0,05±0,001	0,041±0,001	0,052±0,001	0,054±0,001
Notes:	p - the probability of the variance in performance relative to the values in healthy (1), patients with uncontrolled (2), partly controlled (3) and controlled asthma (4)			

This result is quite significant, since it is known that zinc deficiency is associated with a decrease of enzymatic antioxidant defense systems and establish an adequate response of the body to the action of allergens in asthma [1, 6, 8, 21].

Determination of copper in serum of children with asthma revealed the presence of severe hypercupremia in all the patients (PN < 0.001). Thus, the highest level of copper was observed in children with UCBA. Thus, accounting (0, 91±0, 03) mg%, it is not only likely to exceed that of healthy (PN<0.001), but similar in patients with a higher degree of control of the disease (P<0.001). Presence of hypercupremia in patients with asthma to some extent can be seen as a defensive reaction of the organism. It is known that copper acts like an antibody (Ig M), hormones and enzymes, as about 90% of this microelement found in plasma and is a part of ceruloplasmin - acute phase protein [2, 6, 10 , 12]. In addition, copper has a slight immunomodulatory effect. An important factor in increasing the concentration of copper in the blood of children with asthma can be considered its competitive antagonism with zinc for the common ligand bonds during fixation.

Analysis of the survey results of the concentration of magnesium in the blood serum of children with asthma found that the content of bioelements in all the examined children was significantly reduced in relation to the comparison group (PN <0.001), and the lowest rates occurred in children with UCBA. Thus, the magnesium levels in children in this group, accounting (4, 06±0, 06) mg%, was significantly lower from that in healthy (PN<0.001) and in patients with PCBA (P<0.05). Clinical manifestations of magnesium deficiency in children with asthma may be a bronchospasm. Magnesium ions inhibit degranulation and

histamine release from mast cells (membrane effect) and the synthesis of leukotrienes, but also influence the status of the tone of the bronchial tree. Functional antagonist of magnesium is calcium. Magnesium ions block the admission of ionized calcium in cells with both extracellular and intracellular depots, as well as inhibit the degranulation of mast cells and provide the relaxation of smooth muscles of the bronchi.

We determined the increasing calcium levels in all the patients with asthma compared with healthy (PN<0.05), and change most clearly observed in children with UCBA. Composing (4,95±0,47) mg% , the rate of calcium levels in children of this group was not only significantly higher than that of the healthy (PN<0.05), but similar in patients with CBA and PCBA (P<0,05).

Pathophysiological significance of violations of cellular calcium homeostasis is that setting the stage for excessive activation of free radical oxidation of proteins and lipids and inhibiting mitochondrial respiration due to changes in mitochondrial membrane potention and a violation of enzyme activity of the respiratory chain and Krebs cycle, takes an active part in the formation of bronchial hyperreactivity syndrome which is an important pathogenetic factor in the development of asthma.

The level of cobalt and manganese in children with asthma is almost no different from that of healthy people.

Thus, our study showed that the content of MaE and ME in the blood of patients with asthma is changed that manifested the decrease in magnesium, zinc with excess of copper and calcium content and a relatively normal performance of cobalt and manganese. The most pronounced changes were observed in children with UCBA. This can be explained by the fact that the hypoxic change and energy shortage in UCBA is most pronounced, and the amount of basic therapy is the largest.

We noted the dynamics of the main indicators of micro and makroelemental status as a result of drug therapy, which is largely determined by its version. Thus, the use of protocol therapy to control asthma in children with UCBA likely induced reduction of copper (P<0.05) and tended to decrease of calcium and increase of magnesium and zinc (Table 2).

Content analysis of bioelement indicators in children with PCBA on a background of standard therapy showed a significant increase in the level of magnesium and zinc, and reducing of copper (P<0.05). Nevertheless, the treatment practically didn't effect on the concentration of calcium levels which remained elevated and was characterized by only a slight tendency to decrease.

In the course of treatment with therapy to control asthma in children with CBA we received the likely reduction of copper (P<0.05) and tendency to decrease of calcium and at the same time increasing of magnesium and zinc (P<0.05).

During the treatment of patients with varying degrees of control over asthma by combined therapy with Beres Drops Plus for correcting violations of bioelements we've got the following results: in patients with UCBA the level of calcium and copper significantly decreased (P<0.01) , and zinc was significantly increased (P<0.01), but did not come back to normal (Table 3).

Regarding the level of bioelements in children with PCBA on the background of the proposed treatment is obvious positive trend in almost all indicators. Thus, under the influence of treatment during convalescence observed significant decrease in magnesium and zinc level (P<0.01). Copper content after this treatment significantly decreased (P<0.01), but the level of calcium had only a tendency to decrease.

In children with CBA after a comprehensive treatment the following changes were observed: significantly higher levels of magnesium and zinc (P<0.01), and the rate of calcium slightly decreased. However, none of the indicators are normalized compared with the corresponding referent data.

These changes suggest that an imbalance of macro- and micronutrients, which takes place at different stages of controlled asthma, expressed in varying degrees.

Table 2: The evolution of the macro- and microelements of children with varying degrees of controllability in the treatment of asthma by the standard therapy (M±m)

Essential elements	Indicator		Healthy [3] (n=12)	P 1-2	P 2-3
	Before treatment[1]	After treatment[2]			
UCBA (n=12)					
Ca, мг%	3,95±0,47	3,01±0,38	1,21±0,42	>0,05	<0,01
Mg, мг%	4,06±0,06	4,16±0,09	6,07±0,03	>0,05	<0,01
Cu, мг%	0,91±0,03	0,72±0,02	0,48±0,05	<0,01	<0,01
Zn, мг%	0,52±0,02	0,79±0,02	2,70±0,12	>0,01	<0,01
Mn, мг%	0,047±0,005	0,05±0,005	0,039±0,005	>0,05	>0,05
Co, мг%	0,044±0,006	0,042±0,005	0,051±0,001	>0,1	>0,1
PCBA (n=23)					
Ca, мг%	1,89±0,59	1,71±0,38	1,21±0,42	>0,05	>0,05
Mg, мг%	4,10±0,15	4,46±0,09	6,07±0,03	<0,05	<0,01
Cu, мг%	0,61±0,02	0,52±0,02	0,48±0,05	<0,01	>0,05
Zn, мг%	0,83±0,02	0,99±0,02	2,70±0,12	<0,01	<0,01
Mn, мг%	0,044±0,005	0,039±0,005	0,047±0,005	>0,05	>0,05
Co, мг%	0,046±0,006	0,048±0,005	0,051±0,001	>0,05	>0,05
CBA (n=18)					
Ca, мг%	1,94±0,59	1,72±0,38	1,21±0,42	>0,05	>0,05
Mg, мг%	5,06±0,04	5,26±0,09	6,07±0,03	<0,05	<0,01
Cu, мг%	0,66±0,03	0,56±0,03	0,48±0,05	<0,05	>0,05
Zn, мг%	1,69±0,08	2,01±0,02	2,70±0,12	<0,01	<0,01
Mn, мг%	0,046±0,006	0,044±0,006	0,039±0,005	>0,05	>0,05
Co, мг%	0,047±0,005	0,047±0,005	0,042±0,001	>0,05	>0,05
Notes:	P - probability of difference of indicators before (1) and after (2) treatment and compared with healthy (3)				

Improved therapy is largely influenced the levels of copper and zinc in blood, while traditional wasn't effective enough relative to correction of these micronutrients in blood. Thus, the use of combined therapy in patients with asthma is likely accompanied by a reduction in calcium (P<0.01). However, as a result of treatment the calcium rate in children with UCBA was still significantly higher than in similar children with PCBA, CBA and healthy .

Regarding the level of magnesium on the background of combined treatment in patients with asthma, the findings indicate a significant increase of bioelements (P<0.01). Thus, in children with CBA we observed the best dynamics of growth compared with patients with UCBA and PCBA. But to the level of reference values in healthy, these figures did not come close in any group of examined.

Dynamics of copper level in the treatment of combined therapy can be described as follows: in all patient groups this figure decreased significantly (P<0.01). However, when comparing the groups of patients with varying degrees of control, it can be stated that the copper content in children with UCBA was still higher than the corresponding figures for children with PCBA, CBA and healthy. A difference index of copper after treatment in groups with PCBA and CBA had only a tendency to decrease.

After analyzing the indicators of zinc on the background of the proposed therapy we received a significant increase of it in all the groups of patients with asthma (P<0.01). However,

comparing patients with UCBA and PCBA, zinc content increased and remained almost at the same level. Instead, the most expressive changes were observed between groups UCBA and CBA and CBA and PCBA (P< 0.01).

Table 3: The evolution of the macro- and microelements of children with varying degrees of controllability in the treatment of asthma by combined therapy (M±m)

Essential elements	Indicator		Healthy [3]	P [1-2]	P [2-3]
	Before treatment [1]	After treatment [2]			
UCBA (n=14)					
Ca, мг%	4,95±0,47*°	2,91±0,38*°	1,21±0,42	<0,01	<0,01
Mg, мг%	4,06±0,06°	5,16±0,09°	6,07±0,03	<0,01	<0,01
Cu, мг%	0,91±0,03*°	0,62±0,02*°	0,48±0,05	<0,01	<0,01
Zn, мг%	0,52±0,02*°	1,79±0,02	2,70±0,12	<0,01	<0,01
Mn, мг%	0,05±0,01	0,05±0,01	0,04±0,005	>0,05	>0,05
Co, мг%	0,04±0,01	0,04±0,01	0,05±0,001	>0,05	>0,05
PCBA (n=24)					
Ca, мг%	1,89±0,59	1,54±0,38	1,21±0,42	>0,05	>0,05
Mg, мг%	4,10±0,15^	5,36±0,09^	6,07±0,03	<0,05	<0,05
Cu, мг%	0,61±0,02^	0,52±0,02	0,48±0,05	<0,01	>0,05
Zn, мг%	0,83±0,02^	1,78±0,02^	2,70±0,12	<0,01	<0,01
Mn, мг%	0,05±0,01	0,04±0,01	0,04±0,005	>0,05	>0,05
Co, мг%	0,05±0,01	0,05±0,01	0,05±0,001	>0,05	>0,05
CBA (n=16)					
Ca, мг%	1,94±0,59	1,62±0,38	1,21±0,42	>0,05	>0,05
Mg, мг%	5,06±0,04	5,76±0,09	6,07±0,03	<0,01	<0,01
Cu, мг%	0,46±0,03	0,49±0,03	0,48±0,05	>0,05	>0,05
Zn, мг%	1,69±0,08	2,01±0,02	2,70±0,12	<0,01	<0,01
Mn, мг%	0,05±0,01	0,05±0,01	0,04±0,005	>0,05	<0,05
Co, мг%	0,05±0,01	0,05±0,01	0,05±0,001	>0,05	>0,05
Notes:	P – P - probability of difference of indicators before (1) and after (2) treatment and compared with healthy (3) * - The probability of the difference between the patients with uncontrolled and partially controlled ; ° - uncontrolled and controlled , ^ - partly controlled and controlled asthma (P<0.05)				

Thus, the data suggest that patients with different asthma control, which in combination of treatment received Beres Drops Plus, compared to patients treated with standard therapy have significantly increased chances of effective control of disease. Especially noticeable trend was in the groups of children with CBA and PCBA.

Taking into account the results of our data on patients with varying degrees of asthma control using the combined therapy a significant reduction of calcium causes the bronchial hyperreactivity. Increase of Magnesium also has a positive effect in all groups of patients, as is involved in the secretion of the tracheobronchial tree and improves neuromuscular conduction. A well-known part of magnesium is necessary for

adequate functioning of the immune system. Thus, an increase of magnesium can lead to improvement of processes of oxidative phosphorylation, glycolysis, mitochondrial respiration and, consequently, reduced hypoxia in asthma [2, 7, 9].

Reduction of copper in all patients with asthma on a background of combined therapy causes the reduction of the inflammatory response in the bronchi.

Reduction of zinc deficiency helps to improve the activity of non-specific and specific immune defense by influencing the activity of pro-inflammatory cytokines, increasing the number of T -lymphocytes, reduction of Ig E and increased Ig A, Ig M, Ig G [3, 9, 12, 15] and prevents the decrease of resistance of the organism common to the patients with asthma [4, 13, 18].

In our opinion, the quoted results indicate the possibility of the introduction of the drug to the complex treatment of asthma, which would allow to achieve better control over the disease compared with the traditional basic therapy.

4. Conclusions

1. Changes in elemental status in asthma form "vicious circle" of violations supported by nutritional deficiency of macro-and micronutrients and already existing pathological condition.
2. Asthma in children have expressed an imbalance of macro-and microelements, which shows a significant increase in the concentration of copper, calcium and magnesium and reducing the amount of zinc in the blood. Thus, the most pronounced changes were in children with UCBA, minimum - in patients with CBA.
3. Inclusion in the treatment regimen of children with asthma of varying severity the drug Beres Drops Plus allows to achieve the likely reduction of calcium and copper, as well as increase of magnesium and zinc level.

Prospects for further research: The promising is clarification and evaluation of role of dyselementosis in the etiology, Pathogenesis and sanogenesis of asthma in children and the development of adequate prevention and treatment.

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