ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Metabolic Disturbances In Children With Respiratory Diseases.

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ABSTRACT

The literature review provides information about the metabolic changes occurring during respiratory diseases in children. An attempt was made to summarize the scientific data on changes of protein, carbohydrate and lipid metabolism in respiratory pathology in order to justify the need for a differentiated approach to the prescription of metabolic correctors, as well as to point to the need to develop the preclinical diagnostic methods for correction of the minor metabolic disorders by arresting the development of the disease. The introduction of new rehabilitation methods for patients in the acute stage of the disease will reduce the percentage of long-term forms and the chronization of inflammatory processes.

Keywords: *children, respiratory pathology, metabolism*

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ISSN: 0975-8585

INTRODUCTION

In the morbidity of children of all ages, infectious respiratory diseases (IRD) occupy a leading position, and their share reaches 68-72% [1-4]. Respiratory infections lead to disorders of the functional state of the child's body, may cause the failure of adaptation and the development of chronic disease. IRD pathogenesis includes both systemic and local inflammatory processes that occur independently, but in dynamics have and expressed synergistic effect. A multivariate analysis has confirmed that the pathogenetic basis of respiratory diseases involves not only changes in the immunological reactivity of the child's organism, but also in the entire homeostasis [5-8]. Modern publications interpret the nature of systemic inflammatory syndrome as a combination and sequence of a number of processes that start with a generalized activation of inflammatory blood cells, which is accompanied by production and accumulation of free radicals, pro-inflammatory cytokines and chemokines in the blood, the development of dyslipidemia and increased local inflammation [9-11]. In this regard, a promising trend in clinical practice is the so-called "metabolic" direction, which is aimed at analysis of impaired metabolic processes at various levels, which form the basis or background for the formation of many childhood diseases [12-15]. The literature describes the changes of certain types of metabolism in respiratory diseases in children, however, their interdependence has not been studied and a comprehensive study has not been conducted. We have attempted to summarize the accumulated and published data on metabolic disorders and to justify the need for a differentiated approach to the prescription of metabolic correctors.

PROTEIN METABOLISM DURING INFLAMMATION. LIPIDS.

One of the central parts of metabolism in human body is the protein metabolism. Protein metabolic disturbance in inflammation is characterized by the predominance of the proteolysis over the processes of proteosynthesis. The main reasons for the protein metabolic disorders in inflammation are determined by several factors, the leading one among which is a massive release of proteolytic enzymes from the damaged parenchymal and stromal cells, as well as from white blood cells. Their activity is significant, since the catalytic optimum of most proteases has acidic pH (in inflammation focus - the metabolic acidosis). This results in the activation of free radical and peroxide reactions accompanied by destruction of lipoproteins and release of protein compounds therefrom, which are degraded and/or denatured. A direct pathogenic effect of the phlogogenic agent, including enzymatic proteolysis, is also important. The initial stage of protein metabolism disorders is the destruction of cell membranes, damaged by phlogogenic factor. Further, the immune (including immunopathological) reactions with protein denaturation of both the own dead cells and the infectious agent is activated. The inclusion of cellular and humoral immune mechanisms allows for detection, destruction and elimination of antigenically alien structures. Proteolysis products serve as a substrate for synthesis of new cellular components instead of damaged ones.

It should be noted that the main component in the pathogenesis of respiratory diseases is hypoxia, which in biochemical terms is an impaired substrate oxidation in the body tissues, leading to an increase in the blood content of biogenic amines. The accumulation of biogenic amines and the manifestation of their toxic effect even at low concentrations are accompanied by increased decarboxylase activity and inhibited oxidase activity with the formation of free ammonia. Inactivation of amines is achieved by their coupling to proteins. The study of protein metabolism disorders, accompanying the respiratory diseases or other inflammatory diseases in children, are few and do not provide a clear view of the implementation of such changes in the cascade of pathogenetic mechanisms, subject to the premorbid background and characteristics of the individual response of patients [16].

As an important factor in the IRD pathogenesis, both the protein metabolism disorders and the activation of lipid peroxidation (LPO), the release of free radicals, destabilizing lysosomes and damaging lungs and vascular intimal cells, and worsening blood rheology, have been discussed [12-14].

Some authors consider, the following chain of events, leading to the development of hyperlipidemia in inflammation, as a possible option: stimulation of phagocytosis - activation of oxygen metabolism - damage to endothelium enzymes - decreased activity of lipolysis - the simultaneous effect on the proteins and lipoprotein (LP) structure, the disturbance of their interaction with lipolysis enzymes, LP catabolism disorders - formation of hyperlipidemia [13].

According to some researchers, a higher effectiveness of the study of the lipid metabolism in various pathologies, including respiratory diseases, can be achieved through an integrated approach, subject to the LP phenotyping as a possible metabolic response of a patient, since each LP class (which are considered as membrane-like supramolecular complexes) performs a strictly defined function. Thus, patients with pneumonia during its acute phase have decrease in the level of cholesterol, accompanied by a simultaneous increase in the content of lecithin and α-lipoproteids and decrease in β-lipoproteids. A number of data confirms that children and adults with a lower cholesterol content had significantly lower content of peripheral blood lymphocytes and total T-lymphocytes [18]. It was established that during the development of acute pneumonia, the neutrophil membranes has significant reduction in the content of easily oxidized phospholipid fractions (phosphatidylethanolamine (PEA), phosphatidylserine (PS)). While the membranes of the lymphocytes, in contrast, show increase in lipid content. As for the neutrophilic granulocytes, which phagocytosis function is based on a "respiratory burst", their functioning involves primarily the phospholipids with a high content of polyunsaturated fatty acids [14]. Perhaps, the leukocytosis and hyperlipidemia have energetic dependence: on the one hand, the neutrophils use lysolecithin and fatty acids to regenerate the membranes, and on the other hand, the regeneration rate of membranes reflects the state of their reactivity. As a result, the formation of a vicious circle is possible: a decrease in high-density LP fractions reduces their protective capabilities, thereby more activating lipid peroxidation, which destabilizes the receptor and intercellular interactions [12,13]. The formation and accumulation of lipid peroxidation products in biological membranes leads eventually to a significant changes and even dysfunction of the latter. At the same time, due to the high biological activity, aldehydes and dialdehydes have the greatest influence [15]. We have observed a unidirectional change in the content of malondialdehyde (MDA) in plasma and red blood cells in patients with acute-phase inflammatory indicators (sialic acids, seromucoid, C-reactive protein, white blood cells, ESR) [18]. Thus, the above data indicate a high importance of lipid metabolism and lipid peroxidation in the cascade of pathogenetic mechanisms of bronchopulmonary process and show the need for in-depth study of leading pathogenetic components of respiratory diseases, in pathological terms of hyperlipidemia.

CARBOHYDRATE METABOLISM. BIOELEMENTS.

There is a direct relationship in the body between the carbohydrate metabolism (CM) and the metabolism of proteins, lipids and minerals [16]. Lability of regulation mechanisms of carbohydrate and lipid metabolism in early childhood creates the preconditions for the emergence of hypo- and hyperglycemic states, an acetonemic vomiting. According to some authors, the disturbances of the carbohydrate metabolism in children with various medical disorders are secondary and associated with the influence of the main pathologic process on this type of metabolism and manifest themselves, in particular, during pneumonia in infants as increased concentrations of fasting blood glucose and lactate based on the degree of respiratory insufficiency. The fermentation of carbohydrate-containing compounds is primarily hydrolytic and is performed by glycosidases. Glycosidases play an important role in various biological processes; they may, for example, have an impact on the specific growth of the transformed cells, on the interaction of cells with viruses, etc. Increase in plasma fatty acids inhibits the activity of key enzymes of glycolysis. The enzymatic reactions are primarily regulated by Ca^{2+} ions, either directly or with the hormonal assistance, often in combination with a special Ca^{2+}-binding protein - calmodulin. An important role in the regulation of the activity of many enzymes is played by processes of their phosphorylation - dephosphorylation. In some diseases, serious disorders of CM occur again. The alimentary hyperglycemia and hyperinsulinemia lead to the development of obesity, which increases the lipolysis and the use of non-esterified fatty acids (NEFA) as an energy substrate. This worsens the utilization of glucose in muscles and stimulates gluconeogenesis. In turn, the excess of blood NEFA and insulin leads to an increase in synthesis of triglycerides and cholesterol in the liver and, accordingly, to an increase in the concentration of blood lipoproteins of very low and low density [16, 17].

In the inflammation focus, the carbohydrate metabolism undergoes characteristic changes leading to the predominance of glycolysis. Activation of glycolysis is accompanied by accumulation of excessive intermediate products of this process, including lactate and pyruvate, in the cells and in the extracellular fluid, which leads to the formation of metabolic acidosis. Causes of carbohydrate metabolism disorders in pulmonary inflammation are primarily the damages to the membrane apparatus and mitochondrial enzymes that occur under the action of both a phlogogenic agent and other factors that are either activated or produced during inflammatory responses, which include free radicals and peroxide compounds, substances with detergent action, lysosomal hydrolases, excess of H+ and other agents. Another important role is played

by increase in Ca^{2+} level, having a significant uncoupling effect on the oxidative phosphorylation. Another important factor is the increase of ADP, AMP and inorganic phosphate in cells, which results in activation of the key (limiting) enzymes of glycogenolysis and glycolysis. In this regard, the proportion of glycolytic ATP resynthesis starts rising in the inflammation focus. Increase in oxygen absorption at simultaneous reduction in the effectiveness of glucose oxidation in the process of tissue respiration results in a decreased ATP level in the tissue. ATP, formed during glycolysis, although insufficiently, but nevertheless can maintain the energy-dependent processes in cells, especially ions transportation of and muscle contractions, and the vitality and functioning of histological elements in the inflammation focus. At the initial stage of inflammation (when many mitochondria retain their structure, and their enzymes maintain kinetic activity), the recovery of normal or near normal tissue oxygenation is accompanied by rapid reduction in the efficiency of tissue respiration, decrease in glycolysis intensity and normalization of energy supply of cellular processes. All the above changes in biochemical composition of the blood affect the homeostatic potential, one of the important components of which is a complete composition of bio-elements (BE) [2, 17, 18].

Bio-elements are not only the components of local lung protection systems, but also participate in the management of the functional cell activity in the development of inflammation and immune response, and the elemental composition of biosubstrates may reflect the prenosological stage of a pathology. The literature contains numerous reports about the role of zinc in the pathogenesis of acute inflammation development through the regulation of the synthesis of nucleic acids, the active form of thymosine, and stimulation of T-lymphocytes. Studies *in vitro* and *in vivo* founded that the most sensitive to the deficit of copper and zinc are T-killers and T-helpers, macrophages and neutrophils, and to a lesser extent - B-lymphocytes, which is manifested in infectious lesions in internal organs, including lungs. These findings are supported by data on the concomitant decrease in the serum concentration of zinc and the generation of reactive forms of oxygen by neutrophil granulocytes in children with recurrent bronchitis [17, 18].

Another noteworthy information is about BE's ability to manage the activity of lipid peroxidation (LPO) and antioxidant protection. It is known that copper, zinc, iron and manganese are part of superoxide dismutase, selenium glutathione peroxidase, catalase and ceruloplasmin (components of intracellular antiradical system), and their deficiency results in the accumulation of free radicals in tissues and is accompanied by T- and B-cell unbalance and depression of xenobiotic metabolism enzymes. During acute stage of the inflammatory process in the lung tissue, a significant decrease in bromine, chromium, strontium, and molybdenum is observed. An interesting fact is that no complete metabolic rehabilitation occurs during resolution of pulmonary infiltration, even in case of uncomplicated pneumonia and clinical recovery of patients [19].

CONCLUSION

The review data indicate the need to find new approaches to the study of the IPD pathogenesis, correction of homeostatic disturbances at both cellular and subcellular levels, as well as the development of preclinical diagnostic methods allowing for correction of the minimum metabolic disorders by arresting the development of the disease. The introduction of new rehabilitation methods for patients in the acute stage of the disease will reduce the percentage of long-term forms and the chronization of inflammatory processes.

ACKNOWLEDGMENTS

The work is performed according to the Russian Government Program of Competitive Growth of Kazan Federal University

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