CLINICAL AND EXPERIMENTAL STUDIES OF METABOLIC THE BODY'S RESPONSE TO CHRONIC EXPOSURE TO COAL ROCK DUST

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Annotation: Anthracosilicosis in miners is caused by chronic exposure to coal dust and is characterized by the progressive development of the inflammatory process, pronounced lipid metabolism disorders, and an immunodeficiency state. The stages of development were revealed in the experiment anthracosilicosis, according to which adequate methods of prevention and correction of disorders caused by prolonged exposure to coal dust are recommended.

Key words: coal-rock dust, anthracosilicosis, immunity, lipid metabolism, pathomorphosis.

Abstrakt. The coal industry, despite the introduction of modern mining technologies, remains an industry with harmful, difficult and hazardous working conditions. Developments The Kuzbass coal basin is characterized by a high degree of dust, as the underground mining method accounts for 56.2% of the total volume. Prolonged inhalation of coal dust (UPP) causes anthracosilicosis (AS), which is one of the most severe and common occupational diseases of coal industry workers. Industry [6]. In the early stages of AS development, it has weak clinical manifestations, hich significantly complicates its timely prevention, diagnosis and treatment. In this regard, it is necessary to study the systemic manifestation of the metabolic response from the moment of the onset of SCP exposure to the body to its chronic manifestation. The present study is devoted to one of the aspects of this great scientific problem. A big scientific problem. The following tasks were set: to evaluate the indicators of humoral immunity and blood lipid profile in miners with A. Using the experimental model of the AU to study the changes in these indicators in the dynamics of the SCP effect. To conduct medical and biological studies of morphological changes in lung tissue in the dynamics of AS development.

Material and methods. 131 miners with AZ and 159 miners without AZ were examined. And From the (control group) mines of the south of Kuzbass. All the surveyed men, aged 40 to 54 years, were miners of sewage treatment plants, sinkers who had worked for a long time (more than 15 years) under the influence of adverse

industrial factors: heavy physical labor, high concentrations of SCP, vibration, noise, unfavorable microclimate. The main and control groups of the surveyed miners were similar in terms of length of service and working conditions. The clinical part of the work was performed in accordance with the requirements of the GCP and the Helsinki Declaration. 360 adult white male laboratory rats weighing 180-200 g were used in the experiment. The animals were kept in standard vivarium conditions in accordance with the international rules "Guide for the Care and Use Animals». Groups: 1 — intact; 2-6 — rats inhaled in the SCP seed chamber (gas-fat brand coal), according to 4 hours daily, 5 days a week for 12.

Biochemical parameters of animal blood and histological condition of lung tissue were studied on 2-, 3-, 4-, 6-, 8- and the 12th week of the seed. Decapitation was carried out in accordance with the "Rules for work using experimental animals" (Order of the Ministry of Health of the USSR No. 755 dated 12.08 1977).

The content of haptoglobin and ceruloplasmin (using the kits "Haptoglobin" and "Ceruloplasmin" manufactured by Sprinreact, Spain), serum immunoglobulins were determined using the immunoturbodimetric method on a photometer 5010 (Germany) A, G, M (IgA, IgG, IgM) using the appropriate company kits PLIVA — Lachema (Czech Republic) weeks. The average dust concentration in all the studied groups was 50 mg/m3. The inhalation method of seeding animals is most adequate for the conditions of coal mines, where the main route of dust entry into the body is the respiratory system. The content of total cholesterol, low-density lipoproteins (LDL-C), high-density lipoproteins (HDL-C) and triglycerides was determined using enzymatic colorimetric method on a photometer 5010 (Germany). using the appropriate kits from Olvex-Diagnostikum (Russia).

The enzymatic activity of succinate dehydrogenase (SDH), alpha-glycerophosphate dehydrogenase cytoplasmic and mitochondrial (α-GFDH cit., α-GFDH mit.) was studied by cytochemical staining followed by microscopic description of blood smears (microscope MS-50, Austria). The level of glucocorticoid activity was determined by the enzyme immunoassay on a Multiscan analyzer (Finland) using Alcor-bio kits.

For histological examination, lung fragments (one from the left lung and an additional lobe on the right) were taken, from which sections 5-7 microns thick were prepared according to generally accepted methods . During histological examination, basic stains were used, as well as specific elastic staining to detect initial fibroplastic changes in tissues and pronounced pathological manifestations, including vascular changes and pneumosclerotic manifestations (Homery silvering, Schiff reagent reaction). Both the basic and additional colors allowed for a clear to determine the presence of carbon pigment particles, immunological and vascular changes of varying severity. Microscopy of histological preparations was performed using a microscopy -

MS-200 (Austria) at magnification of the eyepiece 10 + 18 and lenses 25, 40 and 100 with water and oil immersion. A comparative analysis of the data obtained was carried out using a semi-quantitative method with the calculation of dust particles, measurement of vascular wall thickness and pathologically altered lung sections. Changes in the bronchial wall and bronchial epithelium were studied. The grade system was used to assess the degree of lymphoid infiltration of the bronchial mucosa's own plate (0 points — no in-filtration, 1 point-minimal, 2 points-moderate, 3 points-massive lymphoid infiltration).

Statistical processing of the study results was carried out by calculating the arithmetic mean (M), the error of the arithmetic mean (m) and was represented as M ± m. The differences between the groups were evaluated using the Student's criterion, differences at $P < 0.05$ were considered reliable.

Results and discussion. For the development of AS, the presence of a certain "critical" in the respiratory organs is necessary the mass of coal dust, the degree of its biological aggressiveness, and work experience in a dusty atmosphere [4, 8]. Literature data indicate that with more than 10-15 years of work experience in dusty conditions, the risk of developing AS reaches 90% [9].

Analysis of clinical data showed that all miners with AS had significantly increased serum levels of ceruloplasmin and haptoglobin. It is known that ceruloplasmin has superoxide dismutase activity, its content increases with the activation of free radical oxidation and inflammatory processes, and therefore it is considered as a protein of the acute phase of inflammation. A significant increase in ceruloplasmin indicates a high activity of free radical oxidative processes in all miners who work for a long time in conditions of exposure to high concentrations SCP confirms the presence of oxidative stress in them. Haptoglobin is also considered as a typical representative of proteins of the acute phase of inflammation and increases nonspecifically in various pathological conditions. An increased background of the above -mentioned proteins in the blood indicates the presence of an inflammatory process in patients with AS. An analysis of the results of our research confirms the fact that, from a pathophysiological point of view, occupational diseases of any etiology can be considered as a manifestation of the depletion phases of the general adaptation syndrome, which is formed under the influence of harmful labor factors [2].

Simultaneously with the presence of an inflammatory process, oxidative stress, and changes in the lipid profile of miners with AS, changes in the humoral link of immunity were revealed, resulting in a significant decrease in serum ID concentration and a tendency to increase IgG (see table). Unfortunately, there is practically no clinical data on early changes in immune status. Histological studies of lung tissue were performed based on the analysis of data obtained during the forensic examination of 38 miners who died in man-made disasters. The average length of service of the victims

was 34.4 years and was represented by the following seniority structure: up to 1 year - 5 people; from 2 to 4 years-3; 5-9 years-8, 10-14 years-6; 15-19-4; 20-24-5; 25-29 years of experience-7 people. The changes in the lungs typical of pneumoconiosis appear almost with the start of the miners' work. At the same time, subatrophic processes develop in the bronchial mucosa and its glands, progressing with the training of workers, as well as sclerosis localized in all structures of the bronchial wall and peribronchially. Some degree of lymphoid and macrophage infiltration of the bronchial wall, the presence of coal dust in macrophages or in clusters, and, in some cases, the formation of granulomas are almost mandatory components [7]. The results of the study indicate the development of vasculitis and perivascular fibrosis in the vessels of the pulmonary artery almost simultaneously with the start of work in dusty conditions.

The data are consistent with the literature [1], which shows that even in the absence of clear clinical and radiological manifestations of the disease, typical pneumoconiotic changes are found in the lung tissue of accidentally killed miners during a pathoanatomic examination.

Experimental models that are close to production conditions and reflect the main pathogenetic links in the dynamics of the development of a particular pathology allow us to assess the state of the body at the initial stages of the development of the disease and identify the stages of its formation.

An analysis of the experimental material shows that, coming through the respiratory organs, UPP, starting from the earliest seed stages, it affects the nature of all metabolic processes occurring in the body of animals.

A significant increase in the level of glucocorticoid hormones in blood plasma in the first two weeks of priming (12.2 ± 1.7 mmol/l in the control, 17.2 ± 2.4 mmol/l in the first week, and 30.3 ± 2.9 mmol/l in the second week) indicates the initiation of a stress reaction in response to a pathogenetic factor.

By the end of the second week of seeding, the content in the blood plasma of rats significantly decreased HDL-C (from 1.0 ± 0.02 mmol/L to 0.6 ± 0.04 mmol/L; $p<0.05$) and LDL cholesterol (from 0.8 ± 0.04 mmol/l to 0.4 ± 0.08 mmol/L; $p<0.05$), as well as total cholesterol (from 1.6 ± 0.04 mmol/l to 1.1 ± 0.03 mmol/l; $p<0.05$), which indicates their active participation in the energy supply system, the sufficiency of which determines the effectiveness of the period of urgent adaptation. A direct confirmation of the activation of energy formation processes was a significant increase during the first two weeks of the SDH level starting from 9.2 ± 0.05 units. Activity in the control is up to 10.5 ± 0.1 units of activity in the first week of seeding and up to 12.5 ± 0.1 units of activity in the second week. A similar level was observed in cytoplasmic α-GFDH (7.8 ± 0.1 units of activity in the control, 9.0 ± 0.1 units of activity in the first week, 9.5 ± 0.2 in the second week of priming) and mitochondrial α-GFDH (7.9 ± 0.1 units activity in the control, 9.8 ± 0.1 units of activity in the first

week, 10.1 ± 0.1 units of activity in the second week of seeding). A significant increase in the concentration of triglycerides during this period (from 0.67 ± 0.1 to 0.95 ± 0.1 mmol/l; $p < 0.05$) indicates the activation of transport forms of fatty acids, which also serve as an important source of energy.

There was no immune response at the initial stage of priming — the level of immunoglobulins was within the physiological norm.

Nevertheless, under experimental conditions And morphological changes were recorded simultaneously in the bronchi, pulmonary parenchyma, vessels of the small circle of blood circulation and the bronchial artery system as early as the 2nd week of priming. First of all, in the form of pronounced alveolitis. Clusters of a significant number of macrophages and in smaller quantities of hemosiderophages were found in the lumen of the alveoli, which indicates an urgent immune response of the tissue to the inhalation of SCP. Bronchospasm is noted in the vessels, intrahepatic lymphoid.

Plasma infiltration, focal thickening of the basement membrane mainly due to edema and fibrosis, deposition of coal dust in the peribronchial spaces. A three-week UPP seed was a factor in the initiation of the inflammatory process, which caused an increase in haptoglobin (from 37.3 ± 2.2 to 53.4 ± 3.4 mg/dl; $p < 0.01$). This fact is consistent with the results of clinical observations in patients with AS. A twofold increase in the ceruloplasmin content in the blood plasma of animals (from 8.2 ± 0.9 to 16.8 ± 0.7 mg/ dl; $p < 0.05$) by the end of the third week of the dust cycle exposure indicates the activation of one of the compensatory stress-limiting mechanisms of cellular protection. Since stress reaction, or the so-called urgent adaptation, enables the body to resist the irritating factor, however, due to its sensitivity, it cannot last for a long time and provide the body with an effective sustainable adaptation to the ongoing negative effects. The level of HDL-C and LDL-C in the blood plasma of experimental animals is not significantly it changes in comparison with the indicators of the two-week seed, remaining significantly below the control values. In our opinion, the level of total cholesterol in the blood plasma of rats, which remained within physiological limits at this stage of the experiment, is explained by significantly higher indicators of its transport forms, triglycerides, compared with the control (from 0.67 ± 0.1 to 0.9±0.07 mmol/l; $p < 0.05$). During the three weeks of seeding, there was only a tendency to increase the level of white blood cells in the blood. Humoral immune the response began to appear more pronounced: the IdA content doubled compared to the control (from 0.12 ± 0.01 to 0.25 ± 0.01 g/l; $p<0.05$). Serum IdA, which functionally acts as the first line of defense on mucous surfaces, prevents the penetration of foreign material. It is no coincidence that its higher content is determined in patients with acute lung abscesses [3]. The tendency to increase the IdM, which has the property of binding microorganisms, indicates readiness for rapid immune response. The response is confirmed by a significantly increased IgG content level (from 2.4 ± 0.06 to 3.0 ± 0.09

g/l; $p < 0.05$).

By the end of the 3rd week of seeding, alveolocytes in animals were detected in lung tissue with general preservation of the respiratory surface. Fullness of the vessels of the microcirculatory bed, peribronchial lymphocytic infiltration with moderate focal fibrosis, proliferation of alveolocytes, and in some animals, the initial stages of granuloma formation, as well as thickening of the bronchial walls. The presence of dust particles was noted in the lumen of the bronchi and alveoli. The continuation of dust exposure for up to six weeks was characterized by further changes on the part of the immune system, manifested in the appearance of immunodeficiency elements.

When a foreign material enters the body, it is absorbed by phagocytes, usually in a non-specific way. The antigen associated with macrophages plays a key role in initiating the immune response carried out by lymphoid cells. Alveolar macrophages are the first immunologically complex cells to absorb inhaled pathogens; they are ideally positioned to interact with the antigen and deliver it to T lymphocytes [11]. In addition, it is known that lymphocytes are surrounded by serum lipoproteins, which exert inhibitory effect by blocking thymidine uptake in lymphocytes. Low-density lipoproteins have the greatest inhibitory ability [10]. The obtained significant decrease in HDL-C in the early stages of seeding and a twofold increase in leukocytes in the blood at a later date indirectly indicate a change in immune reactivity. A significant increase in IdM (from 0.36 ± 0.01 to 0.5 ± 0.01 g/l; $p < 0.05$) is a direct confirmation of this, since it is known that during the immune response at first IdM-class antibodies appear, being the main receptors for antigens on the surface of mature B cells. This fact is an indicator of one of the primary immunodeficiencies caused by the absence of a ligand on T helper cells and, therefore, the inability to transmit a post-stimulation signal to B lymphocytes to switch the synthesis of immunoglobulin M to the synthesis of immunoglobulins of another class [5].

Significant decrease in serum IdA (from 0.12 ± 0.01 to 0.07 ± 0.002 g/l; $p < 0.05$) also indicates the formation of immune deficiency, which, as a rule, contributes to the attachment of respiratory infection. Against the background of the appearance of elements of immunodeficiency by the end of the sixth week of SCP seeding, a significant increase was noted a twofold increase in the number of leukocytes in the blood and haptoglobin (from 37.3 ± 3.1 to 49.2 ± 2.6 mg/ dl; $p < 0.01$). Nevertheless, the relatively favorable metabolic picture and the absence of changes in the content of IgG, the main immunoglobulin, accounting for about 75% of the total amount, indicate that at this stage of the development of the pathological process it has not yet passed into a chronic state. This fact is confirmed by the stabilized blood lipid profile level up to the 8^{th} week of the experiment. The six-week UPP seed caused aggravation of morphological changes in the lungs in the form of bronchospasm, pronounced peribronchial fibrosis, dysatelectasis on the respiratory surface with a sharp thickening

of the interalveolar septa due to the proliferation of fibroblastic cells. A large number of coal dust particles were observed in the lumen of the bronchi and alveoli. There was hyperplasia of lymphoid follicles in the peribronchial lymph nodes and signs of sinus histiocytosis in the marginal sinuses. By the twelfth week of seeding, the inflammatory process had transformed into a chronic one disease. This is indicated by an almost twofold decrease in haptoglobin levels compared to those of the six-week seed, the values of which were significantly lower even than the control values (37.3 ± 2.2 mg/dl in the control, 49.2 ± 2.6 mg/dl in six-week-old animals, 26.0 ± 2.0 mg/dl; $p < 0.05$ in twelve-week-old animals).. The aggravation of the condition manifested itself in dyslipidemia, in which the level of triglycerides significantly increases (from 0.67 ± 0.1 to 0.9 ± 0.09 mmol/l; $p < 0.05$), and the level of total cholesterol significantly decreases (from 1.6 ± 0.04 to 1.3 ± 0.06 mmol/l; $p < 0.05$). At the same time, the LDL-C level drops by 4 times compared with the control (from 0.8 ± 0.04 to 0.2 ± 0.02 mmol/l; $p < 0.01$). Anti-inflammatory interleukins have been found to reduce the synthesis and secretion of cholesterol and LDL protein (apo-B) in the liver, and also activate LDL-C receptors, promoting their uptake by the liver and excretion from the bloodstream [11]. At this time of priming, the experimental animals showed a pronounced state of immune deficiency: the level of IdA decreased by 1.5 times, and IgG – by 1.6 times, compared with the control values.

The histological condition confirmed the onset of irreversible changes lung tissue, in which a decrease in the respiratory surface was detected due to the formation of atelectasis with foci of pneumosclerosis, perivascular and peribronchial sclerosis, moderate to severe, in bronchioles-hyperplasia of goblet cells with the formation of papillary structures of the mucous membrane, in peribronchial spaces, in the sclerosis zone, areas of detached bronchial epithelium, focal angiomatosis, the presence of dust particles and mucus in the bronchial lumen.

Conclusions. 1. The chronic form of anthracosilicosis manifests itself in a tense state of the body's adaptation mechanisms and is characterized by the progressive development of the inflammatory process, pronounced disorders of lipid metabolism, immunodeficiency, and morphological changes in lung tissue that appear almost with the start of mining operations. Subatrophic and sclerotic processes The bronchial tubes progress as the workers become more experienced.

2. Anthracosilicosis develops in phases: 1-2 weeks of coal dust seeding are characterized as a phase anxiety, which is provided by urgent adaptive mechanisms (increased hormonal and metabolic activity, energy supply systems, and macrophagal processes); 3-8 weeks of priming is the resistance phase, which includes mechanisms of long-term adaptation in the form of activation of the enzyme, immune system, antioxidant protection, and morphologically compensatory manifestations in the form of active absorption of carbon particles. Dust by phagocytes, preservation of the

respiratory surface alveolocytes, fullness of vessels of the microcirculatory bed. The depletion phase, registered from the 12th week of seeding, is characterized by a state of immune deficiency, dyslipidemia, and irreversible changes in lung tissue in the form of atelectasis with foci of pneumosclerosis.

3. The conducted research allows us to conclude that when inhaling coal-rock dust, it is necessary early anti-inflammatory therapy followed by immunomodulatory correction to maintain the resistance of the body's endogenous adaptive mechanisms.

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