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Comparative analysis of immunoglobulins in case of combined exposure of dust-radiation factors at remote period

Abstract: One of the most radiosensitive functions of human and animals body is immunological reactivity. A characteristic feature of the radiation exposure is the long-term preservation of damages in individual links of the immune system and associated remote effects and complications. Recently, particular interest is the combined effect of radiation and non-radiation factors on the immune system. In our example, coal dust and various doses of radiation in a remote period had been considered. The aim of this research was to study the effect of low and sublethal doses of irradiation and coal dust, as well as in separate and in combined effects to the immunoglobulin indices in animals in experimental conditions at remote periods.

Six series of experiments had been performed on 60 male rats of Wistar line: group I - intact, group II - rats that inhaled coal dust, group III – exposed to gamma irradiation in a dose 0.2 Gy, IV – exposed to gamma irradiation in a dose of 6 Gy, V group – experienced the combined effect of low dose of radiation and coal dust, VI group - exposed to the combined effect of sublethal dose of radiation and coal dust. Analysis of the researsh results showed that rats exposed to combined dust-radiation factor at remote period had significant changes, which were characterized with the decrease of Ig A and Ig G and increase of Ig M. Ionizing radiation in combination with coal dust at the remote period had more apparent effects, and dominant agent was ionizing radiation.

Keywords: radiation, coal dust, immunoglobulins, remote period, combined effect

Introduction. Essential factor of environmental pollution in certain regions of Kazakhstan is connected with nuclear weapons tests, which were carried out on the territory of Semipalatinsk, Pavlodar and Karaganda regions that covered the territory of 18,500 km^2. More than 450 powerful nuclear tests had been carried out for 40 years in Semey nuclear test site. In comparison with Hiroshima, the power of nuclear weapons had exceeded 2.5 thousand times [1,2]. Regardless the fact that the test site had been closed 25 years ago, people, who were born in the period of radiation tests and received different doses of radiation, still live and work in these regions. Ionizing radiation at different doses at remote period leads to significant health disorders, especially the oppression of congenital and acquired humoral and cellular immunity [3]. Radiation irradiation of the whole body at doses >2 Gy causes various clinical symptoms, higher doses can be so severe that they become life-threatening. The most dramatic effects of radiation exposure were caused by nuclear weapon explosions [4]. The effects of high dose of radiation lead to late and secondary polyorganic deficiencies, activate the systemic inflammatory response [5].

It was shown in animal experiments that radiation damages increased in doses from 2 to 10 Gy, which led to severe hematopoietic damage, and in some animals the chances of survival were quite small [4]. Low dose of radiation causes genetic changes, oncogenesis, as well as physiological changes with decreased immune system [6] and increased cellular stress [7]. On the other hand, low dose of radiation induces biopositive and bionegative effects, thereby reducing carcinogenesis, prolongs life expectancy and enhances fertility [8,9,10].

Kurjane N. and his colleagues evaluated people who received a low dose of radiation during the liquidation of the consequences of the Chernobyl Atomic Power Station. After 10-14 years the level of IgM in workers was increased, and vice versa, IgG was reduced [11]. Decreased levels of IgA, IgM, IgG were detected [12, 13] in another research work which conducted among radiology employees exposed to low dose of radiation for a long time.

Coal mining is an important branch of the world and prolonged inhalation of coal dust during production causes pneumoconiosis, silicosis and respiratory diseases, which are occupational diseases

of the respiratory system of miners [14,15,16]. High concentrations of coal dust in the organism cause changes at the molecular, cellular and histopathological level [17]. Clinical and experimental studies of Fomenko D.V. and his colleagues showed a change in immune reactivity in animals with prolonged exposure to coal dust, thereby causing a chronic inflammatory process [18]. Athracosis - slowly developing lung fibrosis, may develop occasionally in people who constantly encounter free silicon oxide, for example, in the mining and recycling of mountain ores, while not taking adequate measures to protect themselves from dust. It is also necessary to take into account the peculiarity of the Karaganda region, which suffered from the former Semipalatinsk nuclear test site. The problem of the combined effect on the organism of ionizing radiation and production factors (dust with a high content of free silicon oxide) has been studied extremely insufficiently. In the some of literatures has date information about the effect of gamma radiation [19,20,21], and occupational dust on the body separately [22,23]. The working conditions of workers in coal production are characterized by a complex of the most unfavorable factors of the production environment, which needs further study with the aim of developing health-improving measures, especially with the altered immune reactivity of the organism (as the long-term consequences of gamma radiation).

That's why, all of the above is the basis for studying the immunological indicator, in particular immunoglobulins and altered immune reactivity (the long-term consequences of gamma radiation) of the organism on harmful effects production aerosols (free silicon oxide - coal dust). The aim of this work is to study effects of low and sublethal radiation doses and coal dust as well as in individual and combined effects in the long-term period on the amounts of immunoglobulins in animals in case of experimental conditions.

Materials and methods

Experimental animals. Experiments on animals were carried out in accordance with the requirements of the Geneva Convention (1990) and the Helsinki Declaration on the Humane Treatment of Animals and Ethical Standards of the Local Ethics Committee (protocol extract of the local ethics committee of the State Medical Academy of Semey town, Protocol No. 2 of November 18, 2016).

To achieve of the setting goal experiments were conducted on 60 white laboratory male rats of the Wistar line, weighing 220 ± 20 g, which were divided into 6 groups: I group - intact, II group - rats that inhaled coal dust of an average concentration of 50 mg/m3 in a seeding chamber daily (4 hours per day) for 12 weeks, III group - exposed to gamma irradiation at dose of 0.2 Gy, IV group - exposed to gamma irradiation at a dose of 6 Gy, V group - experienced combined effect of low dose of radiation and coal dust, VI group - experienced the combined effects of sublethal dose of radiation and coal dust.

Gamma Irradiation. The animals were once irradiated 90 days before the research at the radiotherapeutic apparatus TERAGAM Co60 (produced by ISOTREND spol. s.r.o., Czech Republic). Prior to the exposure, there was topometric and dosimetric preparation of the experimental animals. To this end, the object was placed on an isocentric therapeutic desk of Terasix X-ray simulator (Czech Republic), which is similar to the therapeutic desk of the γ- irradiator by its construction and parameters. After displaying on a screen, the image slices of the irradiated animals were directly input in the planning system through a computer network connection using a digitizer. Isodoses were calculated using the "PlanW-2000" planning software, and the topometric and dosometric map with technical parameters and planned radiation doses was obtained. The animals underwent exposure to whole-body γ-radiation in a single dose 0.2Gy: SSD – 97.2 cm, SAD -100,0 cm, 40x40 cm field, t=13 sec, in a single dose 6Gy: SSD 97.2 cm, SAD 100.0 cm, 40×40 cm field, t=352 sec (SSD is the distance from the source of ionizing radiation in the apparatus to the conditional centre of the irradiated abnormal focus; SAD is the distance from the ionizing radiation source to the nearest surface of the irradiated object). During the exposure, animals were placed in a specially engineered organic glass cage, each rat in an individual compartment.

Inhalation exposure by Coal Dust. Inducing anthracosis in rat models using a specific inhalation exposure chamber. The experimental animals were placed into cone-shaped compartments, with their vertices attached to the side walls of the exposure chamber. The inhalation exposure device allowed to uniformly disperse the coal dust in the breathing area and maintain the required

dust concentration in the chamber with the help of an automatic analyzer. Coal dust used in the experiment was preliminary comminuted on a vibratory disintegrator. The final disintegration to the fractions, similar to aerosol dispersion in the working zones air, was performed manually in an agate mortar.

Measurement of immunoglobulins. IgA, IgM, IgG immunoglobulin content was determined in all animals by radial immunodiffusion on agar gel according to Mancini [24]. The obtained results underwent statistical analysis differences were estimated using Student's t-test.

Results and discussions. The results of studies are shown in Table 1, which shows that the concentration of IgA in the peripheral blood is increased to 4.33 $\pm$ 0.44 ($p < 0.05$) after exposure to coal dust. In animals irradiated with ionizing radiation at dose of 0.2 Gy, on the contrary, the concentration is significantly reduced, when compared with the second group, where the IgA content of those exposed to low dose of radiation showed 2.96 $\pm$ 0.15 ($p < 0.05$). Under the action of a sublethal dose of radiation, the level reached 1.65 $\pm$ 0.17 ($p < 0{,}001$), which tends to decrease by 2 times, in comparison with the first group. The same case was observed with IgG, but more pronounced changes in indicators. In coal-struck animals, IgG concentration was almost 2 times higher than the control values, comparing with the indicator 8.89 ± 0.68 ($p < 0.05$). In animals in the groups III and V, after radiation exposure with low and sublethal dose, the IgG level rapidly decreased from 2.34 $\pm$ 0.42 ($p < 0.05$) to 2.0 $\pm$ 0.13 ($p < 0.01$) or almost 2.5 times compared with the first group.

Table 1 – Indicators of immunoglobulins (Ig) in exposed animals in case of separate exposures of low, sublethal radiation dose of coal dust in the long-term period (90 days)

№	Indicator	I group	II group	III group	IV group
		Control	Coal Dust	γ-radiation 0,2Gy	γ-radiation 6Gy
1	Ig A g/l	3,31±0,30	4,33±0,44 *	2,96±0,15 ^{o}	1,65±0,17*** ^{ooo}
2	Ig M g/l	4,27±0,30	4,36±0,34	3,30±0,35 * ^{o}	5,93±0,28 ** ^{o}
3	Ig G g/l	5,27±0,72	8,89±0,68 *	2,34±0,42 * ^{ooo}	2,0±0,13 ** ^{ooo}
*Note: Differences from group I are statistically reliable: * - p<0,05, ** - p<0,01, ***- p<0,001. Differences from group II are statistically reliable: ^{o} - p<0,05, ^{oo} - p<0,01, ^{ooo} - p<0,001.*					

As for the level of IgM, in the II group, i.e. in animals after the coal seed, no significant changes are observed, compared with the intact group. Under the influence of gamma irradiation at dose of 0.2 Gy, the concentration of IgM was reduced in comparison with the indication of group I from 4.27 $\pm$ 0.30 to 3.30 $\pm$ 0.35 ($p < 0.05$). In turn, the sublethal dose of ionizing radiation activated the production of IgM, which increased the concentration to 5.93 $\pm$ 0.35 or 1.4 times ($p < 0.01$).

Next, the combined effect of coal dust and ionizing radiation (small and sublethal) was studied in the long-term period on the level of immunoglobulins in two groups (Table 2).

In animals with the combined effect of coal dust with low and sublethal dose, i.e. in the V and VI groups, an opposite trend was observed in the content of immunoglobulins compared to each other. It is necessary to note a special change in the level of IgM, which is significantly higher in comparison with immunoglobulins A and G, where the ratio of IgA, IgM, IgG is about 1: 5: 3. IgM level did not differ significantly with the combined effect of coal dust and low dose of radiation, With the combined effect of coal dust and sublethal dose of radiation, an indicator of 6.15 $\pm$ 0.68 ($p < 0.01$) was established, which is increased by 37-44% compared to the other groups.

As for IgA and IgG, with the combined effect of dust-radiation factor, their content in the blood serum is significantly reduced in comparison with other groups. If we compare the combination of coal dust with low dose and sublethal dose of radiation, then when combined with low dose, the IgG concentration is 4.70 $\pm$ 0.32 ($p < 0.01$), which showed a difference of 2.1 times. This is more than combination of coal with high radiation dose, which in turn shows significant decrease in concentration with respect to the intact group. It should be noted the comparative indicator of the combined effect of coal dust and radiation with indicators of group II, in which the IgG concentration was increased by almost 47.1% (8.89 $\pm$ 0.68, $p < 0.05$) compared to the group V, and in the group VI, ie, when coal was combined with sublethal dose of radiation, the indicators were reliably reduced to 75.1% (2.21 $\pm$ 0.19, $p < 0.001$).

Table 2 – Indicators of immunoglobulins (Ig) in exposed animals with combined effects of low and high radiation dose and coal dust in the long-term period (90 days)

№	**Indicator**	**I group**	**II group**	**V group**	**VI group**
		Control	Coal Dust	Coal Dust+0,2Gy γ-radiation	Coal dust+6Gy γ-radiation
1	Ig A г/л	3,31±0,30	4,33±0,44 *	2,53±0,18 * ^{oo}	1,52±0,10 *** ^{ooo}
2	Ig M г/л	4,27±0,30	4,36±0,34	4,49±0,34	6,15±0,38 ** ^{o}
3	Ig G г/л	5,27±0,72	8,89±0,68 *	4,70±0,32 ^{ooo}	2,21±0,19 ** ^{ooo}
*Note: Differences from group I are statistically reliable: * - p<0,05, ** - p<0,01, ***- p<0,001. Differences from group II are statistically reliable: ^{o} - p<0,05, ^{oo} - p<0,01, ^{ooo} - p<0,001.*					

If we compare the individual effect of low dose of radiation and its combination with coal dust, then when combined, the IgG content decreased in 2 times. As for the comparative effect of sublethal dose of radiation, which was acted on animals separately and combined with coal dust, there were no significant changes between them.

The identical case was observed with IgA, in which the blood level was 1.7 times higher with the combined effects of coal dust with low dose of ionizing radiation with respect to radiation at dose of 6 Gy (1.52 ± 0.10, $p < 0.001$). If we compare them with control animals, the IgA content in their blood decreased from 1.1 times (group V) to 2.4 times (group VI), which shows oppression of IgA level in combined exposure to coal dust and radiation. It is necessary to note the comparative data of IgA in the combined action of coal dust and ionizing radiation with other groups of animals under study, where significant deviations in their level were detected. Comparative analysis of the combined action of coal dust and radiation with separate effect of coal dust showed that in group V there was pronounced suppression of production of IgA by 42% (2.53 ± 0.18, $p < 0.05$), and in the group VI, there was also significant decrease in IgA by 65% (1.52 ± 0.10, $p < 0.001$).

When assessing the individual effect of radiation in different doses, compared to them in combination with coal dust, IgA concentrations did not show any significant changes (8-14.5%).

According to the obtained data , there are significant changes in the state of the humoral link of the immune system with respect to the combined effect of coal dust and radiation. IgA concentration in blood serum was reliably reduced by the combined effect of coal dust with low dose of irradiation by 23.6%, the lowest level was revealed when coal was combined with sublethal radiation dose to 54% compared to the control group. Animals exposed to radiation also showed tendency to decrease the content of IgA in the serum of peripheral blood [25]. In the II group, i.e. in animals harvested with coal dust, IgA is markedly increased. This is explained by the fact that serum IgA functionally acts as the main protection on mucous surfaces, preventing the penetration of foreign material. In patients with acute lung abscesses, its higher content is determined not by accident [26]. As for IgG immunoglobulin, when it was exposed to coal, it increased significantly, in other cases there was an active decrease in the level with respect to healthy animals, especially this can be explained by the switching of production of IgG by B lymphocytes in patients with allergic diseases [27]. Radiation and combination of radiation with coal dust leads to the degradation of this class of immunoglobulins up to 75.1%, which can be explained by the fact that IgG is about 75% of the total amount of immunoglobulin, and its reduction proves the transition of the pathological process to chronic. There is a slight change in IgG only in the group V.

Also, it is important to note that the level of immunoglobulin IgM had reliable tendency to increase concentration in blood serum. Practically in all studied groups, except for the III group, i.e. in irradiated animals with low radiation dose, a high IgM value was detected, especially when combined exposure to coat dust and sublethal dose of γ-irradiation.

High level of IgM [28] was found in healthy individuals who lived for a long time in the Semipalatinsk region and were born before 1963. Characteristic feature of the increase inimmunoglobulins in the blood are signs of the development of autoimmune reactions from effects of carbon-containing dust, which in the next turn can lead to pneumoconiosis.

If we compare the concentrations of immunoglobulins with the combined effect of coal dust with small and sublethal dose of radiation, then special changes are noticed. First of all, the combination

of coal dust with low dose of radiation gave an indication closer to the control values, but different from the combined effect of coal dust with sublethal dose. This is explained by the biopositive property of low dose of radiation, which reduces the toxic properties of coal dust with combined effect [29].

Secondly, we can note that in the late period there was significant oppression of the concentration of immunoglobulins A and G in blood serum under the action of sublethal dose of gamma irradiation alone and in combination with coal dust, and in turn IgM showed pronounced activation. Decrease in the IgA and IgG content indicates immunodeficiency, which is accompanied by chronic inflammation and high tendency to neoplasm with high irradiation with ionizing radiation. The tendency to increase the concentration of IgM, which has the property of binding microorganisms, indicates the readiness for rapid immune response. Significant increase in IgM content confirms this fact.

According to results of the study, it can be undoubtedly established that more pronounced activation of immunoglobulins (IgA and IgG) is observed after inhalation by coal dust, in comparison with separate exposure to radiation in different doses. Similarly, there was an increase in IgA and IgG levels and stable level of IgM in the work carried out among male workers in the coal mine, which may have been systemic response of the body to dust particles [30]. In general, there was tendency to lower levels of all immunoglobulins (IgA, IgM, IgG) only in group III. Decrease of IgM level increases the resistance of B cells, but the body's ability to resist infections decreases. Lowering IgA and IgG complementary to IgM deficiency leads to immunodeficiency and forms autoimmunity in group III of rats [31,32]. With regard to groups IV, V, VI, they demonstrated generalization of IgM and content suppression of IgA and IgG. Increased level of IgM, reduced level of IgA and IgG cause Hyper-IgM syndrome. In the most part genetic damage can cause hyperproduction of IgM, the cause may also be infringement of B-cells [33,34]. Activation of humoral immunity occurs due to an increase in the level of immunoglobulin M (IgM), which forms the primary immune respon se to various pathogens. Thereby the humoral immunity [35] activates with inflammation of the respiratory system and cancer diseases.

Conclusions. Thus, significant changes were detected in experimental rats subjected to combined dust-radiation factor in the long-term period. Changes were characterized by decrease in IgA and lgG and an increase in IgM. Ionizing radiation in combination with coal dust in the distant period has more pronounced effect by the formation of the immunodeficiency syndrome. The dominant agent in developing pathology was ionizing radiation in case of combined effect of two factors, especially at high doses.

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Сравнительный анализ иммуноглобулинов при сочетанном воздействий пыль-радиационного фактора в отдаленном периоде

Аннотация: Одной из наиболее радиочувствительных функций организма человека и животных является иммунологическая реактивность. Характерной чертой радиационного воздействия является длительное сохранение повреждений в отдельных звеньях системы иммунитета и сопряженных с ним отдаленных последствий и осложнений. В последнее время особый интерес представляет комбинированные воздействия радиационного и нерадиационного факторов на иммунную систему. В нашем примере рассмотривались угольная пыль и разные дозы радиация в отдаленном периоде.

Целью исследования являлось изучение влияния малой и сублетальной дозы облучения и угольной пыли как и в отдельном, так и сочетанном воздействии в отдаленном периоде на показатели иммуноглобулинов у животных в экспериментальных условиях.

Выполнены 6 серии опытов на 60 крысах-самцах линии Вистар: I группа - интактные, II группа - крысы, вдыхавшие угольную пыль, III группа – подвергшиеся гамма-облучению в дозе 0,2 Гр, IV - подвергшиеся гамма-облучению в дозе 6 Гр, V группа - испытавшие сочетанное воздействие малой дозы радиации и угольной пыли, VI группа – испытавшие сочетанное воздействие сублетальной дозы радиации и угольной пыли. Анализ результатов исследования показал, что у крыс, подвергавшихся сочетанному пыле-радиационному фактору, в отдаленном периоде были выявлены значительные изменения, которые характеризовались снижением IgA и IgG, и повышением IgM. Ионизирующая радиация в сочетании с угольной пылью, в отдаленном периоде оказывал более выраженное воздействие, доминирующим агентом являлась ионизирующая радиация.

Ключевые слова: радиация, угольная пыль, иммуноглобулины, отдаленный период, комбинированное воздействие.

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Шаң-радиация факторының қосарлы әсерінің кейінгі кезеңіндегі иммуноглобулин-дердің салыстырмалы сараптамасы

Аннотация: Адам мен жануарлар ағзасының радиосезімталдылығының басымырақ қызметтерінің бірі болып, иммунологиялық раективтілік болып табылады. Бұның өзгерістерін сәулелік зақымдалудың клиникалық симптомдарының пайда болуына дейін, объективті әдістермен анықтауға болады. Радиационды әсердің өзіндік ерекшеліктеріне, иммунитет жүйесінің жеке буындарында зақымдалудың ұзақ сақталуы және сонымен қоса кейінгі кезең зардаптары мен асқынулары жатады. Сонғы уақыттарда, радиационды және радиционды емес факторлардың иммунды жүйеге қосарлы әсері ерекше қызығушылық тудыруда. Біздің жұмыстың үлгісі, кейінгі кезеңдегі көмір шаңы және әртүрлі дозадағы радиация. Зерттеудің мақсаты аз және сублетальды дозалы сәулеленудің және көмір шаңының дербес және қосарлы әрекетінің, жануарлардың иммуноглобулиндер көрсеткіштеріне кейінгі мерзімдегі әсерін тәжірибелік жағдайда зерттеу болып табылды. Тәжірибе 60 Вистар аталық егеуқұйрықтарына 6 серия бойынша жүргізілді: I топ - бақылау, II топ – көмір шаңымен тыныс алған егеуқұйрықтар, III топ – 0,2 Гр дозалы гамма-сәулеленуге ұшыраған топ, IV топ - 6 Гр дозалы гамма-сәулелену қабылдаған топ, V топ - аз дозалы радиация мен көмір шаңының қосарлы әсеріне сынақталаған топ, VI топ – сублетальды дозалы радиация мен көмір шаңының қосарлы әсерін сынаған топ. Зерттеу нәтижелерінің сараптамасы көрсеткендей, шаң-радиация факторының қосарлы әсеріне ұшыраған егеуқұйрықтарда, кейінгі мерзімде маңызды өзгерістер анықталды. Олар IgA және G мөлшерінің төмендеп, IgM деңгейінің жоғарлауымен сипатталды. Иондаушы радиацияның көмір шаңымен қосарлы әсері өте айқын әрекет көрсетті, әсіресе иондаушы радиация басымды агент болып табылды.

Түйін сөздер: радиация, көмір шаңы, иммуноглобулиндер, кейінгі кезең, қосарлы әсер.

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