

Acute radiation syndrome

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Summary:

Ionizing radiation has a mutagenic effect. Depending on the absorbed dose, age and general health condition, it may cause specific organismal changes and disturbances of varying degree. This paper describes different forms and symptoms of radiation sickness and its impact on respective systems of the human body.

Key words: radiation sickness, haematological syndrome, clinical symptoms.

As the effect of short-term high-dose ionizing radiation exposure to the whole body, symptoms of tissue and other internal organ damage occur. In consequence, it leads to a gradual development of complex, systemic pathological syndrome, called radiation sickness. Besides, ionizing radiation also induces mutagenesis, i.e. it causes mutations. Specific changes and disturbances of varying severity may occur in human body, depending on the age, general state of health and, in particular, the absorbed dose. Depending on the radiation amount absorbed by the human body, different forms of radiation syndrome can be distinguished. Main classification includes chronic and acute radiation syndrome. There are also other methods of classification. Some authors identify severity grades of acute radiation syndrome, distinguishing mild, moderate or severe form. Other authors classify acute radiation syndrome considering the received dose and time of exposure, identifying three types of manifestation: haematological (haematopoietic), gastrointestinal and neurovascular syndrome, also referred to as fulminant. Haematological syndrome occurs at the absorbed radiation dose of 0.8 Gy to 8 Gy. Gastrointestinal manifestation develops due to radiation dose ranging from 8 to 20 Gy, and the neurovascular form appears as a result of doses exceeding 20 Gy.

Haematological (haematopoietic) syndrome

The hematopoietic manifestation of acute radiation syndrome (ARS) is a combination of symptoms resulting from hematopoietic and immune system damage, and dominates the clinical picture after whole body irradiation with doses from 0.8 to 8 Gy of gamma radiation, or equivalent doses of X-ray or neutron radiation. Damage to these systems is of much greater intensity after irradiation with higher doses. In such case, however, symptoms of damage to other systems (gastrointestinal, nervous, cardiovascular) may appear, which leads to death of an irradiated individual before symptoms of hematopoietic system damage develop. In some cases, the above mentioned forms of ARS may occur simultaneously.

Medical intervention is particularly important in haematological manifestation of acute radiation syndrome, as the treatment may be crucial for patient's prognosis. Clinical picture of this form of manifestation includes four stages:

- 1) First stage characterized by initial (prodromal) symptoms (also called primary reaction symptoms).
- 2) Latent stage.
- 3) Stage of fully developed clinical symptoms.
- 4) Recovery or death

Based on the intensity (severity) of clinical symptoms, the following clinical forms (grades) of radiation syndrome are identified:

- mild, when the absorbed dose of radiation ranges from 0.8 to 2 Gy;
- moderate, when the radiation absorbed dose ranges from 2 to 4 Gy;
- severe, when the radiation absorbed dose is from 4 to 6 Gy;
- very severe, when the absorbed dose of radiation reaches a value from 6 to 8 Gy.

The above mentioned clinical stages of the radiation syndrome may vary in time of duration and the severity, depending on the clinical manifestation form. Data regarding the duration of particular clinical stages, as well as time to primary reaction and its severity constitute an important factor for further prognosis. Accordingly, initial period symptoms of mild radiation syndrome occur in 2-3 hours after irradiation, mainly as nausea, single vomiting, short-lasting headaches, anxiety and a lack of generalized skin reaction. These symptoms last from a few to over a dozen hours. Latency period is three to four weeks. In some cases, the third stage develops subsequently, however, without severe clinical symptoms. Coexisting diseases or injuries (mechanical, thermal) may result in a long and severe course. Death occurs only in case of complications.

Moderate form of radiation syndrome is characterized by the onset of initial period symptoms within 1 to 2 hours after irradiation and lasts 1 to 2 days. The main symptoms are: constant headaches, vomiting, insomnia, mild irritation of the skin. The duration of the latent stage ranges from 16 to 25 days (3 weeks on average). The period of full manifestation of clinical symptoms is from 3 to 4 weeks, the period of recovery – from 1 to 2 months. Fatal outcome is estimated at 20-50%. Deaths occur with a full development of clinical symptoms and complications.

In case of severe manifestation of radiation sickness, the symptoms of the initial period appear within 30 to 60 minutes following irradiation and last for 1 to 3 days. Primary symptoms are: agitation, persistent vomiting, loss of appetite, severe headache, elevated body temperature, evident skin irritation, possible diarrhea. Latency period lasts from 8 to 17 days (approximately 2 weeks), the period of full manifestation of clinical symptoms lasts up to 4 weeks, period of recovery is from 3 to 6 months. Estimated fatal prognosis is more than 50%.

A very severe form of acute radiation syndrome is characterized by extremely intense symptoms

of initial period beginning within 30 minutes after irradiation. These symptoms include persistent vomiting, loss of appetite, severe permanent headache, high temperature, severe skin irritation and diarrhea.

Latency period ranges from 6 to 8 hours. Full development of radiation sickness symptoms follows after a short latency period. Patients die within 5 to 12 days. Mortality is up to 100%.

Clinical symptoms.

The initial period of hematological manifestation of acute radiation syndrome, as already mentioned, can last from several hours to 2-3 days. During this period, agitation is observed, usually followed by apathy and general weakness, as well as headaches and dizziness. Severe forms may lead to impaired consciousness. In very severe cases, meningismus with nuchal rigidity and positive Kernig's and Brudzinski's sign is observed. Mucous membranes are hyperemic, small hemorrhages occur occasionally, as well as transient skin hyperemia and elevated body temperature or fever. Apart from nausea and vomiting, other gastrointestinal symptoms may appear, such as abdominal pain and diarrhea. Polyuria occurs, and abnormal components are found in urine test, such as protein, glucose and acetone. Women suffer from menstrual disorders and uterine bleeding. The initial period gradually gives way to the latent stage. Patient starts improving, appetite returns, as well as the ability to sleep. Nervous system symptoms diminish. Despite a general improvement, the hematopoietic system shows the aggravation of lymphopenia, leukopenia and thrombocytopenia.

Alterations of haematopoiesis are characteristic for the third stage of acute radiation syndrome. They appear even with low doses of radiation, which cause no symptoms of damage to other systems or organs. In the first period of radiation sickness, as a result of haematopoietic stimulation, there is an increase in all morphological blood components, except for lymphocytes. Leukocytosis measured within the first 36 hours correlates with the severity of radiation sickness. Lymphopenia is the most sensitive indicator of irradiation and can be noticed on the first day at radiation absorbed dose of 0.25 Gy. Peripheral blood lymphocyte level decreases immediately after irradiation, and the decline reaches a maximum after a few days and, to some extent, is proportional to the absorbed dose. After sub-lethal doses, lymphocytes may completely disappear from the blood. According to M.R. Dambro, decrease in lymphocyte count may be proportional to the absorbed dose, and the total count of lymphocytes measured 48 hours after exposure determines the severity of radiation syndrome:

- over 1500 - trivial exposure (mild form of radiation syndrome),
- over 1000 - survival without treatment (mild form of radiation syndrome and some cases moderate forms of radiation syndrome)
- from 500 to 1000 - survival, if treatment is implemented (moderate and severe forms of radiation syndrome),
- from 100 to 400 – lethal, if bone marrow cannot be transplanted (severe and very severe form of radiation syndrome),
- below 100 - certain death (gastrointestinal or cerebral manifestation).

Normalization of lymphocyte count is a slow process, lasting up to several months. After initial leukocytosis in the first 36 hours after irradiation, at the end of the second period (latent stage), and especially in the third period of radiation syndrome evolution, an increasing leukopenia is observed, positively correlating with the absorbed dose and reaching its maximum within 40 days after exposure. It reverses slowly, and values below normal range often persist for several months. Blood smear test reveals the presence of immature cells with segmented multilobular nuclei, reflecting the pathological cell division. Toxic granulations and vacuolation of granulocytes are frequently observed.

In the third period of radiation syndrome, but not earlier than 3-4 weeks from onset of the disease, the red blood cell count decreases gradually. This is an effect of reduced production or medullar aplasia, as well as increased hemolysis or bleeding. The absence of reticulocytes within 48 hours following exposure is an evidence of high-dose irradiation. The reason for this is a significant radiosensitivity of erythroblasts. In severe forms of radiation sickness, erythrocytopenia can be as low as 1 million of red blood cells with hyperchromic type of anemia (embryonic type of blood cell formation and megalocytosis are observed). Osmotic resistance of blood cells decreases. Signs of regeneration are observed during the recovery period, mostly regarding red blood cells. Increasing reticulocytosis corresponds with returning efficiency of bone marrow. Serious reticulocyte crisis, up to 70%, is observed, correlating with the severity of anemia. Megaloblastic reaction also occurs with megalocytes and megaloblasts appearing in the peripheral blood. Red blood cells count increases gradually - the average cell value is increasing, while the osmotic resistance remains decreased.

Gastrointestinal system

Immediately after irradiation, all dyspeptic symptoms occur: nausea, vomiting, heartburn, xerostomia, loss of appetite – all resulting from increase of gastric juice acidity. Abdominal pain and diarrhea

may appear. In the third period, after asymptomatic latent stage, a prolonged reduction of gastric juice secretion is observed with decreased acidity and reduced fraction of free HCl. Tongue becomes dry and coated. Along the gastrointestinal tract (mouth, esophagus, bowels) ulcerations occur, which can create a route of entry for infection or cause perforation.

Due to reduced tension of intestine muscular layer, bowels may become partially enlarged, which can lead to invagination and symptoms of adynamic bowel obstruction. Intestinal epithelium becomes atrophic and exfoliates, food absorption is significantly impaired. Diarrhea appears, often with blood traces. Degenerative changes can be found in the liver.

Mucous membranes and skin

During the first period of radiation syndrome, irritation of conjunctiva is noticeable. Oral, gingival and palatal mucosa is red and swollen, hypersensitive to cold and heat, prone to mechanical damage. In severe cases ulcerations, abscesses and necrosis occur. Erosive inflammation with atrophy expands in mucosa of the upper respiratory tract. Initially, the skin becomes remarkably pale. Later on, it gets dry due to the atrophy of sweat glands and even with high temperature it does not perspire. In case of radiation absorbed dose of 3.5 Gy, it comes to a hair loss. In moderate manifestation, epilation begins in third week of disease and it is limited to the most exposed areas. Hair regeneration starts in 1-2 months after epilation. Due to hair follicle atrophy, the hair growth occurs only in less exposed areas of the skin. New hair is thin, dry and turns grey occasionally. Irradiated parts of the skin remain hyperpigmented for a long time.

Respiratory system

The initial stage is characterized by a mild dyspnea and tachypnoe. Second phase is asymptomatic. During the third period, all symptoms of acute inflammation in the upper and lower respiratory tract occur. In addition, impaired bronchial tone and expectoration difficulties often lead to bronchopneumonia. Severe cases are prone to radiation pneumonitis with pleural reaction.

Cardiovascular system

Initially, tachycardia and hypotension is seen. Second stage is asymptomatic. Third period includes cardiac enlargement and quiet heart sounds. Occasionally, systolic murmur can be heard. Electrocardiography reveals decreased voltage in all leads, S-T segment depression and intraventricular conduction defects.

Urinary system

During the initial period, polyuria is observed with pathological components (proteins, glucose, acetone) appearing in urine samples. These symptoms are a consequence of renal damage manifested by increased tubular permeability. During the third stage, the amount of urine is reducing. Urine specific gravity decreases and proteins appear. A significant number of erythrocytes and lymphocytes is found. Glomerular changes embracing capillary endothelium and some focal thickening of basement membrane occur.

Reproductive system

Sensitivity to radiation of the human gonads is as follows:

- abnormal gametogenesis in females at a dose of 2-3 Gy,
- abnormal gametogenesis in males, 3-6 Gy,
- permanent infertility in women, 5-6 Gy,
- permanent infertility in men, 9-12 Gy.

Moreover, menstrual dysfunction and intrauterine bleedings occur. Miscarriages occur in pregnant women in 1-2 week of pregnancy. In 2-7 week of pregnancy, it comes to major anomalies of embryonic development.

Additional laboratory tests reveal increased urea and creatinine levels in blood serum, resulting from intense protein disintegration. This process is also responsible for increased urinal concentration of free amino acids which are normally absent: proline, tryptophan, phenylalanine, alanine, aspartic acid. Composition of plasma proteins, particularly in the third stage, is subject to significant alterations. Albumin proportion decreases considerably, whereas globulin percentage elevates. Electrophoresis showed an increase in α - and β - globulins (with an evident reduction of gamma globulins).

Based on studies, it was found that tissue content of nucleic acids is reduced. RNA/DNA ratio also becomes imbalanced, with a significant reduction of the latter. Due to DNA disintegration, urine elimination of beta-aminoisobutyric acid (BAIBA) is increased. Within a few hours after irradiation, elevated levels of glycemia are found, and the glucose

concentration curve resembles the one in diabetes. As a result of glycogen depletion, lipid metabolism is disturbed. Oxidative processes are reduced causing lipid metabolism limitations with increased production of ketones. This may lead to ketonuria. Mineral metabolism is also disturbed. Chloride and sodium levels are significantly reduced.

Gastrointestinal syndrome

Gastrointestinal manifestation develops at radiation absorbed doses of 8-20 Gy. The radiation absorbed dose of 12 Gy immediately provokes gastrointestinal symptoms of acute radiation syndrome. The symptoms of the initial period include strong nausea and persistent vomiting, watery diarrhea and abdominal pain. The clinical presentation of intestinal mucosa damage occurs 5-7 days following latency period. Hemorrhagic diarrhea, fever and adynamic intestinal obstruction appear – so called post-injury shock. Small intestine loses its structure; heavy gastrointestinal bleeding, diarrhea and abdominal pain occur within three days. Haematopoietic manifestation develops subsequently. Death occurs as a result of blood loss or sepsis, usually caused by Gram-negative bacteria. Patients who survive this phase die at later stages due to bone marrow suppression. Death occurs within several days, mortality is up to 100%. Damaged intestines become a route of entry for infections, and immune system collapse enables bacteremia and toxemia. According to many authors, water-electrolyte imbalance is the most important factor of gastrointestinal syndrome and mortality.

Cerebral syndrome (fulminant).

Cerebral manifestation occurs with doses exceeding 20 Gy. According to the recent data from the literature, this form of radiation syndrome should be rather referred to as neurovascular syndrome. Primary changes include the damage of blood vessels, mainly epithelium of capillary, leading to irreversible shock. Cerebral hypoxemic changes are only the final effect of these processes. Death occurs within several hours to a few days after exposure.

Tremor, ataxia, vomiting, arterial hypotension and seizures occur after 15-30 minutes of asymptomatic period, resulting in death. Mortality is 100%.

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