

PATHOPHYSIOLOGY AND CLINICAL SYMPTOMS OF ACUTE RADIATION SYNDROME

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Abstract

Introduction: The use of radiation sources in various areas of life generates the risk of accidents and radiation disasters. The increase in terrorist threats as well as the risk of an outbreak of new armed conflicts carries the risk of using radioactive materials by terrorist groups and the military. Exposure to high doses of radiation and absorbing above-threshold doses by victims may cause acute radiation syndrome (ARS), as well as some distant effects. Personnel of the State Emergency Medical System (EMS) will be the first professional medical team in the process of providing assistance to such victims. The effects of further medical treatment in the hospital will depend on EMS's first response, radiological triage and initial interventions taken.

The aim: To present pathophysiology and clinical symptoms of acute radiation syndrome in the context of the medical practice of the EMS.

Material and methods: For the purpose of this publication, an analysis of literature on the subject of the mechanism of ionizing radiation and its effects on the human body was performed. The work is focused on the interpretation of research results and their presentation from the EMS's perspective.

Results: The publication presents the impact of ionizing radiation on the body, the mechanism of damage to cellular structures and its consequences for individual organs and systems. ARS's clinical (hematopoietic, intestinal, cerebrovascular) syndromes were discussed in detail, paying attention to radiation doses, the sensitivity of individual systems and organs, the dynamics of individual phases, as well as the ability to recognize and assess the severity of their progression by EMS personnel.

Conclusions: The knowledge of pathophysiology, and ARS's symptoms and dynamics is important to respond correctly to radiation incidents. This knowledge allows for efficient organization and emergency management during rescue operations. The increase in the risk of radiation incidents and radiation disasters generates the need for appropriate preparation of emergency rescuers, in particular, of the medical personnel of the State Emergency Medical Services.

Key words

ionizing radiation,
deterministic effects,
acute radiation syndrome

INTRODUCTION

Radiation is the form of energy in the event of which different physical phenomena occur. Ionising radiation is one of many kinds of radiation. The ionisation is created when the radiation is absorbed by matter. There are 5 basic forms of ionising radiation: alpha radiation, beta radiation, gamma radiation, X-radiation and neutron radiation [1]. Each of the radiation type manifests its individual characteristics and properties. Tissue exposure to the same dose of different radiation measured in Gy units (grey) has dramatically different biological effects. Thus, it was necessary to introduce a term of an equivalent dose which is measured in Sv (sievert). $Sv = W_R \times Gy$ where W_R

represents the quality factor of a radiation type which is characteristic for each radiation type. The factor W_R equals more than 1 for gamma radiation and up to 20 for alpha radiation [2]. The authors use Sv and Gy units interchangeably assuming that the biological effect of the described doses is equipotent.

Ionising radiation is present in the environment and its source is cosmic radiation and radioisotopes produced in the Earth's crust (background radiation). The natural ionising radiation (background radiation, cosmic radiation) averages to 2.4 mSv per annum [3]. Humans give off radiation as well due to radioactive potassium present in the body. Taking advantage of radiation brings the risk of accidents and catastro-

phes. Over the years several incidents causing severe impact on health occurred. The Chernobyl disaster in Ukraine in 1986, a radiation incident in Mexico City in 1962, the Goiânia incident in Brazil in 1987 and the Fukushima Daiichi nuclear disaster started by the tsunami in Japan in 2011 [4–6]. Radioactive materials are also used for the military and terrorist purposes. The polonium-210 was used to poison Alexander Litvinenko - a Russian dissident and a former officer of the Russian Federal Security Service (FSB) and KGB [7]. Radioisotopes and various devices emitting radiation such as X-ray devices, CT scanners commonly used for medical purposes may pose some risks of exposing patients to high doses of radiation. For instance, in Białystok five women undergoing radiotherapy to treat breast cancer were given higher doses than intended as the device was not functioning properly [8].

THE AIM

The authors show the pathophysiology and clinical signs and symptoms of the Acute Radiation Syndrome (ARS) in order to discuss and draw attention to the difficulty of providing medical help to patients.

REVIEW

PATHOPHYSIOLOGY OF ARS

Clinical symptoms are divided into early and late deterministic effects (dose related) and stochastic ones (not dose related). Non-stochastic effects are either local esp. Cutaneous Radiation Syndrome (CRS) or systemic esp. Acute Radiation Syndrome (ARS). The authors aim to discuss ARS.

Acute Radiation Syndrome is caused by irradiation of the whole body or a significant portion of it with a penetrating dose greater than 1Gy [9, 10]. ARS is characterised by signs and symptoms that are manifestations of tissue damages to the organs and organ systems. The mechanism of radiation damage to the tissue varies. Not only can radiation have a damaging effect on a genetic material but also on a cytoplasmic membrane and active sites of enzymes (catalase, peroxidase). Time of ionising radiation penetrating a mammalian cell is 10-14 of a second while a DNA molecule is 10-18. The exposure of 1 Gy causes ionisation of 10⁵ in every cell of 10 μm in diameter. Consequently, 1-2 Gy dose of ionising radiation causes about 1000 DNA single-strand breaks and around 40 DNA double-strand breaks [10]. There is a direct and indirect effect of ionising radiation on a cell. Water radiolysis is an indirect process which results in the production of a hydrogen ion H⁺ and a hydroxide ion OH⁻, which further produce free radicals (H₂O₂,

O₂). These particles cause damages to the genetic material of a cell. Radiation has an indirect effect on DNA as a result of Compton Effect /Compton Scatter and photoelectric effect. [11]. If the damage to the DNA is beyond repair with high doses of ionising radiation, it can induce the cell death or its lysis. If the damage cannot be repaired and the suppressor genes and oncogenic genes are exposed to the ionising radiation, the neoplastic transformation can be started [12]. Irradiation damages to the DNA are as follows: double-strand breaks, single-strand breaks, damages to cellular proteins, cell membrane lipids and enzymes. During the mitotic phase cells were shown to be highly sensitive to the ionising radiation in G2 phase and M phase of a cell cycle. The radiation induces mitotic delays and slows down transition from G2-->M phase and G1-->S phase [2]. It is due to p21 protein that is produced in the CDKN1A gene expression [13]. Those delays allow the cell to repair DNA damages induced in the course of radiation. The expression of GADD45 gene being a marker of various physiological and environmental stressors was observed. The expression of this gene results in the production of protein which affects p21 protein that halts the cell cycle at the checkpoints in order to repair damages incurred in the genetic material.

As mentioned above, irradiation indirectly results in the production of free radicals (H₂O₂, O₂). Free radicals affect the genetic material and their products can cause changes in DNA chain and distort its structure that may result in mutations. One of those products is 8-Oxo-2'-deoxyguanosine (8-oxo-dG) that manifests highest mutagenic potential. It is also a diagnostic tool to assess the radiation risk and a reliable oxidative marker of DNA damages. A urine test may allow to assess the risk of mutation of the genetic material after radiation exposure [14, 15].

Radiation may also change chromosomal structures. The frequency of chromosomal aberrations is one of the most reliable markers of DNA damages being a result of ionising radiation [16]. Aberrations may be divided into chromosomal and chromatid ones. The above mutations are the result of ionising radiation and are irreversible. The radiation induces translocation mutations in which segments of chromosomes get mutually rearranged and dicentric mutations in which segments of chromosomes get rearranged and result in the production of 2 chromosomes; one of 2 with two centromeres and the other lacks a centromere. Translocations are mutations passed on to children while dicentric ones are non-inherited. Thus, their significance is decreasing as the cell proliferation occurs [17]. High instability of

karyotype (changes within the structure of chromatids or chromosomes) has been observed in cell colonies that survived the X radiation exposure to 2Gy or more than that [18].

Ionising radiation may cause damages to lipids and proteins. Free radicals especially a hydroxide ion interact with fatty acids causing the peroxidation of membranes. Consequently, the membrane of lipids and proteins stops functioning and loses its integrity. Malondialdehyde (MDA) is the marker of polyunsaturated acids peroxidation in the cells, and the MDA concentration in blood platelets has showed a significant increase after the exposure to ionising radiation [19].

By exposing cellular proteins to radiation, free radicals make the protein chains break where proline occurs. Consequently, no functional protein is produced [20]. The level of a peripheral protein and messenger RNA (mRNA) of an intercellular adhesion molecule 1 (ICAM-1) exposed to ionising radiation has been tested. It was shown that the exposition of ICAM-1 on the surface has grown by 0,125 and 0,25 Gy. The findings suggest that low doses of radiation affect post-transcriptional regulation of mRNA ICAM-1 which causes exposure to ICAM-1 protein [21]. It may serve as a diagnostic tool to assess the risk of the patient exposed to low doses of radiation.

Radioresponses of tissue are dependant on types of tissue exposed to radiation. There are two models of tissue organisation: Flexible (F-type) model and Hierarchical (H-type) model. According to the law of Bergonie and Triondeau "tissues appear to be more radiosensitive if their cells are less-well differentiated, have a greater proliferative capacity, and divide more rapidly." The main characteristic of H-type model is high proliferation rate which suggests a high level of stem cells. Three compartments can be distinguished in H-type model. The first one is the stem cell compartment consisting of stem cells capable of proliferation and self-renewal to maintain their number. Stem cells of the intestinal epithelium, stem cells in the basal layer of the epidermis and bone marrow stem cells are examples of the stem cell compartment. The next type is amplification compartment, in which cells mature, replicate and differentiate. Cells of the basal layer of the epidermis and erythroblasts are examples of the second type. Another group is called post-mitotic compartment consisting of fully differentiated cells such as the cells in the surface layers of epidermis, cells at the top of villi of intestinal mucosa and mature circulating blood cells.

Flexible model (F-type model) consists of identical cells with tissue-specific function and have capacity

for cell renewal. Connective tissue, nervous tissue are liver parenchyma are some examples of F-type model [22]. Table 1 presents differences between two models of tissue. For better understanding of the impact of irradiation on F-type model certain terms have been used: W_T - the tissue weighting factor for tissue or organ and the effective dose. W_T accounts for variable radiosensitivity of organs and tissues to radiation. The radiation weighting factor (W_R) is used to determine differences in biological effects depending on different radiation types exposed to a human body. The absorbed dose (Gy) is equivalent to the absorption of one Joule (J) of energy per kilogram (kg) of material [23]. W_T, W_R and the average absorbed dose allows to calculate the equivalent absorbed dose (Sv) that leads to the effective dose. The effective dose is a sum of all equivalent doses absorbed by tissues and organs from both internal and external exposure. It represents health risk to the whole body even if only particular parts of a body were exposed to irradiation [24]. The unit of measurement for effective dose is the sievert Sv.

The term critical organs was introduced due to different organ sensitivity to irradiation. The term refers to the organs most vulnerable to a given isotope or type of radiation. When external exposure to radiation in the form of gamma or X-rays occurs, the critical organs are bone marrow, gonads and lens of the eye. When alpha-radioactive isotopes are administered orally, the critical organ is intestines and the intestinal mucosa where isotopes are accumulated [20]. An absorbed isotope of iodine accumulates in thyroid which is the critical organ. Other isotopes such as polonium, strontium or radium accumulate in bones and bone marrow. Similarly, isotopes taken into the body via inhalation of radioactive fallout particles were observed to accumulate in liver, spleen and bone marrow [25].

The term of a tissue tolerance dose represents the radiation dose an organ can receive without adverse effects. The tissue tolerance dose may differ for different tissues and organs depending on a radiation type. The tissue tolerance dose refers to late effects of radioactive exposure [26]. The tolerance dose TD5/5 represents the radiation dose that would result in less than 5% risk of severe damages within 5 years after irradiation [27].

CLINICAL PICTURE OF ARS

Acute Radiation Syndrome is subdivided into 3 subsyndromes: the hematopoietic syndrome, the gastrointestinal syndrome and the neurovascular syndrome. Each subsyndrome is comprised of four clinical phases: prodromal, latent, manifest illness,

final one. The signs and symptoms of the prodromal phase appear within 1-3 days after the exposure and are characterised by vomiting, nausea, fever, headache and early skin erythema. The onset of vomiting is also related with the absorbed dose and can be observed within few minutes after a high dose exposure. The prodromal phase has been presented in Table 2. The second phase of ARS is a latent phase depending on individual patient's sensitivity and the absorbed dose and may occur from 2-20 days following the exposure [28]. It is a delusive phase characterised by improvement of symptoms. The paramount indicator of ongoing changes is the changing level of lymphocytes and granulocytes in peripheral blood. Those changes depending on the absorbed dose are presented in Table 4. The most sensitive marker of radiation exposure is the change of a lymphocyte level which is used to triage the casualties of radiation incidents. The third phase (a critical phase) occurs within 21-60 days following radiation exposure and its symptoms are characteristic for each syndrome [28]. The final phase is either recovery or death depending on the absorbed dose, the dose rate and the heterogeneity of exposure (how much and which part of the body has been exposed) and individual patient's sensitivity to radiation.

THE HEMATOPOIETIC SYNDROME

The hematopoietic syndrome results from the exposure to doses of 2-3 Gy [29]. The initial predominant symptom of doses less than 10 Gy is lymphopenia within 6-24 h [30]. An absolute lymphocyte count that remains within 50% of normal during the first week following exposure suggests an exposure of less than 1 Gy and a survival rate is above 90% [9]. It is believed that a dose of 0.95 Gy reduces the population of stem cells to 37%. For this reason, the hematopoietic syndrome may be developed with radiation exposures below 1 Gy [31]. The onset of signs and symptoms depend on the physiological cellular loss rate of cells and the dose-dependent reduced supply of cells from the depleted proliferating compartments. [34] Genotoxic and other specific toxic mechanisms, leading to aplasia, cell apoptosis or necrosis are involved in radiation hematoxicity. The clinical signs and symptoms of the hematopoietic syndrome are the result of reticulocytopenia, anemia, granulocytopenia, monocytopenia, and thrombocytopenia [32]. There is a subpopulation of stem cells that displays more resistance to irradiation than other cells and are crucial to restore morphotic elements after exposure to doses up to 6 Gy [34]. Initially, laboratory tests show a decline in the number of lymphocytes and transient increase in the number of granulocytes [34]. After their lifespan of about 7-24

h, granulocytes disappear from the blood. The higher the dose, the earlier the disappearance of granulocytes [29]. There has been observed a gradual reduction in the number of circulating leukocytes, platelets, erythrocytes over time. The onset of signs and symptoms that appear in the hematopoietic syndrome depends on the physiological cellular loss rate of circulating cells [34]. In the hematopoietic syndrome bone marrow failure leads to death. [34].

THE GASTROINTESTINAL SYNDROME

The onset of early and mild symptoms of the gastrointestinal syndrome such as nausea and vomiting occur at doses below 1,5 Gy [35]. More severe symptoms develop at doses of 5-12 Gy due to the radiation damage to stem cells leading to apoptosis within 3-6 h after the exposure [36]. Damaged cells are replaced with other stem cells provided not all stem cells are damaged, otherwise the crypt dies. The substantial loss of crypts leads to villous atrophy followed by the ulceration within 3-9 days after the exposure which is the time needed for the restoration of villi. Radiation-induced enterocyte damage leads to its reduction. It has been observed that lower doses cause nucleus and chromatin swelling while higher doses lead to changes in biochemistry of cytoplasm and impair cell membranes. It has a negative effect on intercellular junctions and enterocytes as it inhibits cell division and disturbs cell membranes. These changes cause disorders of absorption and increased intestinal secretion. Irradiation disturbs intercellular integrity and causes disorders of intestinal mucus production as a result of a reduced number of goblet cells. Consequently, impaired barrier function of the gastrointestinal tract results in the passage of bacteria through the intestinal wall into the bloodstream. The gastrointestinal signs and symptoms usually start 48 hrs after exposure but that depends on the radiation dose. The signs and symptoms include nausea, vomiting and headaches that are followed by fever over time. In the symptomatic phase there are the following symptoms: appetite disorder, the feeling of fullness of upper abdomen, salivary gland swelling, ileus (resulting from ulceration and necrosis of the bowel wall leading to stenosis), bloody stools, dehydration, electrolyte imbalance and sepsis. All the symptoms may lead to multisystem organ failure and death [37].

THE CEREBROVASCULAR SYNDROME

The cerebrovascular syndrome occurs with doses greater than 10 Gy [9]. Due to radiation exposure, radiation neurotoxins are produced. Radiation Toxins of CV ARS are defined as glycoproteins with the molecu-

lar weight of RT toxins ranges from 200-250 kDa and with high enzymatic activity. Neurotoxins cause damages to endothelial cells that leads to their increased permeability. Furthermore, the disruption of a blood-brain barrier and the disorder of cerebral circulation occur. Most likely neurotoxins act on the receptors NMDA, AMPA, 5HT1, 5HT2, 5HT3 that leads to their overactivation and trigger the death cell mechanism [32]. Apart from cellular damages caused by irradiation, brain tissue is also affected. There has been noticed a decrease in the population of oligodendrocyte progenitors which leads to the reduction of mature oligodendrocytes and consequently demyelination of myelin sheath around nerves. Moreover, the process of apoptosis of oligodendrocytes has been noticed to be activated. Irradiation leads to the proliferation of astrocytes and microglial cells [38]. Neurological deficits such as reduced deep tendon reflexes, ataxia and corneal reflexes have been observed [9,10]. These symptoms are followed by cerebral edema, impaired consciousness resulting from disturbances of cerebral blood microcirculation. The consequence of brain edema is an increase in intracranial pressure. Progressive respiratory distress along with hypotension resulting from impaired cerebral blood supply and neural conduction in brainstem leads to patient's death within 2 days after exposure [10].

DISCUSSION

As a result of the Chernobyl accident the diagnosis of ARS was initially considered for 237 persons based on symptoms and the diagnosis of ARS was confirmed in 134 persons. The persons were exposed to radiation doses of 0,8-16 Gy. There were 28 short term deaths of which 95% occurred at whole body doses in excess of 6.5 Gy. After the Fukushima accident no ARS level of radiation was observed [40, 41]. It was found that the radiation incident in Mexico City in 1962 was caused by cobalt-60 that had been found unprotected in the garbage dump and brought home. Four people died from exposure to radiation [42]. In Goiânia in 1967 a capsule with radioactive isotope of caesium-137 was stolen from the abandoned hospital. As a result, 46 persons were radiated, 4 persons died and 28 required skin graft or amputations [43].

Each and all radioactive contamination accidents and disasters are a great source of information about the influence of ionising radiation on a human body. Studies have shown that radiation sensitivity is not the same for the general population. Men are more vulnerable to radiation effects than women [44]. Children, elderly people and people with hereditary

diseases are the most vulnerable. Children's higher sensitivity to radiation is due to a higher mitotic activity and dynamic increase in cell number. Owing to the fast growth, there is less time for radiation-induced DNA damages to be repaired [45]. Higher sensitivity to radiation has been observed due to the higher proliferation activity and less cellular differentiation [46]. Persons (over 60) have increased radiation sensitivity than adults (below 60). The increased radiation sensitivity of aging cells may be the consequence of already dysfunctional systems dealing with radiation-induced damages. There are changes in elderly persons' bodies that enable radiation-induced damages. One of them is the oxidative stress arising from aging that causes an increase in number of free radicals and induces DNA, protein and lipid damages. Another one is telomeres shortening in aging cells which leads to genome instability caused by disruption of the cell cycle checkpoints. Moreover, DNA repair-deficiency has been observed. Telomere dysfunction, DNA damage and persistent response to radiation induce cell aging process as the cycle is stopped irreversibly [47]. Studies showed that 18 genetic disorders have radiation hypersensitivity. Patients with such hereditary disorders as Ataxia-Telangiectasia Syndrome, Nijmegen Breakage Syndrome, LIG4 Syndrome (Ligase IV Syndrome), Seckel Syndrome, Werner Syndrome and Fanconi Anaemia show the highest radiosensitivity. The most common radiation effect on patients with the above disorders are DNA double-strand breaks [48].

Exposure to ionising radiation at doses above threshold values lead to different subsyndromes of ARS. The absorbed dose is not the only marker of patient's damages and patient's survival rate. Whether a patient will suffer from ARS depends on patient's individual radiosensitivity, age, general health condition, extent and length of radiation exposure. It is crucial for survival to stop radiation exposure and perform radiation triage. Absorbed doses above 1 Gy will probably lead to ARS and assessing absorbed doses allows to predict type of ARS and induce proper medical response management.

CONCLUSIONS

Proper EMS responses followed by hospital treatment substantially increases patients' survival rates. The understanding of ARS pathophysiology and all clinical manifestations of every ARS subsyndrome improves effectiveness and accuracy of medical responses provided and allows for better hospital treatment of radiation incidents' casualties.

Table 1. Differences between H-type and F-type models of normal tissues.

Properties	H-type model	F-type model
Examples	Bone marrow, skin epidermis, gastrointestinal and urinary tract epithelium, testicular epithelium	Connective tissue, nervous tissue, liver parenchyma, liver parenchyma
Proliferative capacity of functional cells	None	Infinite
Time of functional damage	Dose-independent	Dose-dependent
Time-scale of expression of radiation injury	Early	Late

Source: Own study based on [10,18,34].

Table 2. Signs and symptoms of ARS prodromal phase.

Signs and symptoms	Mild (1-2Gy)	Moderate (2-4Gy)	Severe (4-6Gy)	Very severe (6-8Gy)	Lethal (>8Gy)
Vomiting	>2h after exposure	1-2h after exposure	<1h after exposure	<30 min after expose	<10 min after exposure
Diarrhea	-	-	Mild (3-8h after exposure)	Heavy (1-3h after exposure)	Heavy (within min after exposure)
Headache	Slight	Mild	Moderate (4-24h after exposure)	Severe (3-4h after exposure)	Severe (1-2h after exposure)
Consciousness	Unaffected	Unaffected	Unaffected	May be affected	Unconsciousness
Body temperature	Normal	Increased (1-3h after exposure)	Fever (1-2h after exposure)	High fever (<1h after exposure)	High fever (<1h after exposure)

Source: Own study based on [49].

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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