Role of Postradiation Genome Instability in Evaluating the Development of Radiation-Determined Pathology in Children After the Chernobyl Accident and Investigation Perspectives

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Citation

Abstract
The role of genetic instability (inferred from cytogenetic parameters of chromosome aberrations) and nuclear DNA repair activity play in radiation-determined diseases (neoplasms, including malignancies; congenital disorders and malformations; and chromosomal disorders) is considered in children from regions varying in extent of soil contamination with cesium-137 after the Chernobyl Accident. (Soil contamination with cesium 137 exceeds 1665 kBq/m²). Children groups of different ages were formed having taken into consideration the data of Chernobyl Accident and birth date of child. On analyzed cytogenetic parameters (different types of chromosome aberrations) and the status of genomic DNA repair. On revealed a significant increase in unpaired (p < 0.05) and paired fragments in children from radiation-polluted regions, number of chromosome aberrations being more significant for the children born in 1988 or later. Our study showed a high DNA repair index for the children born before the Chernobyl disaster and it’s decreasing in children born later (more extremely – in children born after 1988). A narrower protein polymorphism (using the individual heterozygosity index) may point to hypersensitivity to an ecopathogenic factor especially in children born in 1988 or later, suggested narrowing an adaptive potential for children whose exposure started during their intrauterine development. Health monitoring in the children showed phase-dependent cytogenetic changes, exposed to radiation, correlated with activity of repair, compensatory, and restorative processes. Along with genetic instability, these changes reflect the individual radiosensitivity and provoke radiation-induced and somatic diseases in children exposed to low-dose ionizing radiation.

1. Introduction

Long-term multiple (continuous) low-dose exposure to an ecopathogenic factor (radiation) involves body systems in long-term adaptation, which can form and transform throughout individual life [1,2]. To characterize genome instability in children...
continuously exposed to low-dose ionizing radiation and to estimate the possibility of de-adaptive responses that clinically manifest as radiation-determined disorders, we studied the cytogenetic parameters and the status of genomic DNA repair as a main protective, compensatory, and restorative system of the body.

2. Characterization of the Child Groups Examined

As of January 1, 2009, there were 104,555 children in Russia who lived in regions polluted with radionuclides, had been evacuated and resettled, or were born to Chernobyl clean-up workers. We examined children from the southwestern Novozybkov region (Bryansk oblast), which was contaminated from the Chernobyl disaster of 26 April 1986 and includes sites where soil contamination with cesium 137 exceeds 1665 kBq/m², thus belong to the compulsory evacuation zone. As a control, we examined children from noncontaminated areas of Bryansk oblast, which were similar in geochemical and economic parameters to Novozybkov region.

The test groups of children from the contaminated areas were as follows: Group 1 included children born before the Chernobyl disaster (156 children aged 9-11 years), Group 2 included children exposed to the total range of radionuclides (including radioactive iodine) in utero and born from 1986 to 1987 (167 children aged 7-8 years), Group 3 included children born from 1988 to 1993 (148 children aged 4-6 years), and Group 4 included children born from 1995 to 2000 (137 children aged 1-3 years). Four control groups were formed according to the case–control paradigm and included 163 children of the same age groups (45, 43, 44, and 31 children, respectively).

Statistical forms of Federal statistical follow up were analyzed:
- No. 12 Data on disease cases number reported in patients residing in the region of medical facility;
- No. 15 Data on medical service of radiation-exposed population in relation to Chernobyl Nuclear Power Plant who should be included in the Russian State Medical Dosimetry Register;
- No. 16 Data on disease cases and causes of death of patients who should be included in the Russian State Medical Dosimetry Register in relation to Chernobyl Nuclear Power Plant.

A statistical analysis of the results was performed using the programs Statistica 6.0 (StatSoft, United States) and Origin 6.0 (Microcal Software, United States). In the case of normally distributed variables, the mean and the standard deviation (SD) or standard error (SE) were calculated for each group. When a variable distribution was other than normal, the median and upper and lower quartiles were computed. A difference was considered significant at p < 0.05.

3. Results and Discussion

Mutagenesis is activated in response to radiation as an ecopathogenic factor. Radiation exposure may act as a trigger and increase the effects of other exogenous and endogenous agents and/or their combinations [3]. Protective, compensatory, and restorative processes arise as a result, depending on the extent and intensity of oxidative stress and the genetic specifics of the stress response.

The children exposed to radiation displayed a significant increase in aberrant metaphases (4.68±0.16 and 2.54±0.18 in control, p < 0.05), as well as in both chromatid (unpaired fragments3.87 ± 0.21 and 1.76 ±0.12 in control, p < 0.05) and chromosome (paired fragments0.79 ± 0.15 and 0.28 ± 0.06 in control, p < 0.05), dicentrics, and rings (0.34 ± 0.01 and 0.06 ± 0.004 in control, p < 0.05) aberrations, which are classified as unstable. Unstable chromosomes revealed unpaired and paired fragments, dicentrics, and rings and stable - deletions and translocations chromosome aberrations. The finding can be explained by the fact that the children were permanent residents of contaminated areas, agreeing with an increase in dicentrics and chromosome rings reported in the literature [4]. The frequency of stable chromosome aberrations (translocations and deletions) in the total group of children from contaminated area did not significantly differ from that in the control group (Table 1).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Children exposed to radiation (N = 608)</th>
<th>Control (N = 163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total chromosome aberrations (frequency, %)</td>
<td>4.68 ± 0.16*</td>
<td>2.54 ± 0.18*</td>
</tr>
<tr>
<td>Unpaired fragments (frequency per 100 cells)</td>
<td>3.87 ± 0.21*</td>
<td>1.76 ± 0.12*</td>
</tr>
<tr>
<td>Paired fragments (frequency per 100 cells)</td>
<td>0.79 ± 0.15*</td>
<td>0.28 ± 0.06*</td>
</tr>
<tr>
<td>Dicentrics and rings (frequency per 100 cells)</td>
<td>0.34 ± 0.01*</td>
<td>0.06 ± 0.004*</td>
</tr>
<tr>
<td>Translocations (frequency per 100 cells)</td>
<td>0.29 ± 0.11</td>
<td>0.14 ± 0.05</td>
</tr>
<tr>
<td>Deletions (frequency per 100 cells)</td>
<td>0.28 ± 0.12</td>
<td>0.17 ± 0.07</td>
</tr>
</tbody>
</table>

* Difference from the control is significant at p < 0.05.

The cytogenetic parameters were compared between the different groups, and the children residing permanently in radionuclide-contaminated areas were found to have higher frequencies (per 100 cells) of unstable (unpaired and paired fragments, dicentrics, and rings) and stable (deletions and translocations) chromosome aberrations. Unpaired and paired fragments were the most common chromosome aberrations in the children (Table 1).
Similar data on the accumulation of somatic chromosome aberrations in children have been reported by Ukrainian researchers [5,6]; and similar observations made in workers involved in cleaning-up activities after the disasters at the Mayak Chemical Combine and Chernobyl Nuclear Power Plant [7].

When children exposed to radiation starting from intrauterine development were isolated from the total sample, the difference in cytogenetic parameters was even greater. (Fig. 1).

Figure 1. Scores of cytogenetic parameters in different age groups of children exposed to radiation («0» - control).

Compared with children of other groups, these children displayed a significant increase in unpaired (p < 0.05) and paired fragments. The difference in the whole number of chromosome aberrations being even more significant for the children born in 1988 or later. In addition, a broader range of cytogenetic structural defects was observed in this group and included isochromatid fragments, centromeric breaks, and chromatid exchanges. The most common stable chromosome aberrations were deletions (D14q) and translocations (B4D) in the children born in 1988 or later and translocations (12;16q23;q11) in the children born from 1986 to 1987. A karyotype analysis revealed higher aneuploidy (trisomy B, C, or D) mosaicism in the children born in 1988 or later. Polyploidy was observed in the children born from 1986 to 1987[8].

The repair system is one of the most important mechanisms protecting the genome. Structural genetic cells can be eliminated as a result of activation of DNA repair. A decrease in spontaneous or induced repair processes is indicative of a lower protection potential and, therefore, a higher individual sensitivity to certain ecopathogenic factors. Repair processes restore damaged and/or lost DNA sequences, thus preserving genome stability. A decrease in gamma- or UV radiation-induced repair points to inadequacy of adaptive, compensatory, and restorative mechanisms [9].

Our study showed a higher DNA repair index for the children born before the Chernobyl disaster and living in contaminated areas as compared with the control children (2.15 ±0.08 vs. 1.73 ± 0.01 p< 0.05). The changes can be regarded as a protective compensatory response to ecopathogenic exposure. However, long-term activation may lead to functional strain and subsequent exhaustion of the protective mechanisms.

Figure 2. Gamma-radiation-induced DNA repair index in children of different groups.
The gamma-radiation-induced DNA repair index of the children who were born from 1986 to 1987 and exposed to radiation in utero was lower than in the control (1.5 ±0.03 vs. 1.73 ± 0.01, p< 0.05). (Fig. 2).

The children born in 1988 and later similarly displayed a decrease in DNA repair index; the decrease was especially significant for the children born five to ten years after the Chernobyl disaster as compared with the control and other groups (1.7± 0.05 vs. 0.80± 0.01, p < 0.05).

Thus, our results indicate that the mutation process remained intense in somatic cells of children from various groups even after a long period of time (5-10 years) after the Chernobyl disaster. While germline mutations cause congenital malformations and hereditary disorders in the progeny, chromosomal mutations in somatic cells lead to genome instability and, consequently, cell dysfunction, various alterations of vital processes, lower functional activity, and a limited adaptation potential [10]. The above changes are possibly indicative of a higher radiation sensitivity and provide a basis for the development of pathological conditions and radiation-induced diseases. The effect of the intense mutation process in children exposed to radiation in utero or born in 1988 or later is exacerbated by a lower capability to eliminate chromosome aberrations (a decrease in gamma-radiation-induced DNA repair index) and a limited adaptation potential (a decrease in individual heterozygosity index). It should be noted that the processes may accompany a normal adaptive cell response to irradiation [11,12]. However, substantial consequences for the body are possible in the case of long-term exposure, if this "normal" response involves a considerable portion of cells (given that the total body is exposed).

Hereditary polymorphism is one of the mechanisms that sustain population variation and human adaptation to various environmental conditions; in addition, it provides the possibility to associate various diseases with certain gene markers.

A narrower protein polymorphism or rare alleles of protein-coding genes may point to hypersensitivity to an ecopathogenic factor. Rare alleles of protein-coding genes tended to increase in frequency in our sample, as was seen mostly for haptoglobin 2 and acid phosphatase B. Higher frequencies of the haptoglobin-2 allele and homozygous 2-2 genotype have similarly been reported for the progeny of people exposed to radiation in Chelyabinsk oblast (Tel’nov et al., 1994).

A decrease in individual heterozygosity index was observed in the children from radionuclide-contaminated areas (Fig. 3).
1999 to 2009 has similarly shown that the incidence gradually increased and was always higher in children exposed to radiation (in 2009, the neoplasm incidence was 859.8 according to Statistical Form no. 16 and 801.7 according to Statistical Form no. 12).

Our health monitoring in the children showed that phase-dependent cytogenetic changes occur in the body exposed to radiation and that their time course correlates with activity of repair, compensatory, and restorative processes. Along with genetic instability, these changes reflect the individual radiosensitivity and provoke radiation-induced and somatic diseases in children exposed to low-dose ionizing radiation.

At the same time, it was not found any health disturbances that permitted us to profound investigations to clarify the mechanisms of radioinduced changes in the children. A preferred model for evaluation are gene networks of p53 protein, which are in relationship with genomic instability, the expression of genes those are controlled by the functioning of p53, will provide an opportunity to assess the risk of radiation-induced diseases (oncological pathology, chromosomal diseases, neoplasms). Nanostring technology one allows to analyze the expression of up to 800 genes for 1 sample. Identifying the most typical changes in gene networks of p53 protein for different generations of children having burn in families of radiation-exposed parents, will make able to create specific panels to improve the diagnostic process.

References


