EVALUATION OF CYTOGENETIC DAMAGE IN NUCLEAR MEDICINE PERSONNEL OCCUPATIONALLY EXPOSED TO LOW-LEVEL IONISING RADIATION*

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The aim of this study was to provide data on genetic hazards associated with occupational exposure to low doses of ionising radiation in nuclear medicine departments. The DNA damage in peripheral blood lymphocytes of medical staff was assessed using the chromosome aberration test. Altogether 120 subjects (60 exposed and 60 controls) participated in the study. The exposed subjects showed significantly higher frequencies of chromosome aberrations than controls. Significant inter-individual differences in DNA damage within the exposed population indicate different genome sensitivity. Age and sex were not confounding factors, while smoking increased DNA damage only in control subjects. This study suggests that chronic exposure to low doses of ionising radiation in nuclear medicine departments causes cytogenetic damage. For this reason, exposed medical personnel should minimise radiation exposure wherever possible. Our results also point to the significance of biological indicators, which provide information about the actual risk for the radiation-exposed individuals.

KEY WORDS: chromosome aberrations, DNA damage, peripheral blood lymphocytes, radioisotopes, risk

Ionising radiation has become an important clinical tool for both medicinal diagnosis and therapy. Currently there are many radiopharmaceuticals in clinical use; ongoing research will undoubtedly result in an increase in the number of such agents (1). As the diagnostic and therapeutic applications of radiopharmaceuticals have continued to grow, the general public’s awareness of the hazards of ionising radiation has increased. The radioactivity administered presents a risk to the patient, which should be balanced against the benefit from obtaining a diagnosis or carrying out a treatment. Furthermore, contact with radioactive tissue from the patient or exposure to radiation emitted from radioactivity retained by the patient presents a risk to hospital staff and to members of the public (2).

Occupational exposure in nuclear medicine departments is mainly related to low doses of particular ionising emissions from radioactive isotopes such as $^{99m}$Tc, $^{131}$I, $^{32}$P, $^{67}$Ga, $^{111}$In, $^{203}$Tl, $^{59}$Fe, $^{57}$Co, $^{51}$Cr, and $^{192}$Ir (3-5). These radioisotopes have unstable nuclei, and dissipate excess energy by spontaneously emitting radiation in the form of gamma and other rays.

Unlike patients, medical staff are usually exposed to much lower doses, but for a longer period of time. All professional and technical staff in nuclear medical facilities are responsible for maintaining radiation exposure at ALARA (as low as reasonably achievable) levels. However, due to the ability of ionising radiation to induce cellular damage, there is some level of risk for the development of genetic damage after radiation exposure.

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To implement proper radioprotection procedures and restrict hazards to human health, it is very important to estimate the absorbed doses in individuals occupationally exposed to ionising radiation (6). The extent of health hazards is difficult to assess. In order to obtain information about the distribution and extent of radiation exposure, different biological methods for dose assessment have been developed. These include the evaluation of DNA mutations, chromosomal aberrations, the induction of micronuclei and sister chromatid exchanges (7, 8). The most fully developed biological indicators of ionising radiation exposure are unstable chromosomal aberrations (dicentrics in particular) that can be detected in samples of peripheral blood lymphocytes (9-11). This method usually complements data obtained by physical dosimetry and is routinely used whenever the individual dosimeter shows an exposure to penetrating radiation above its limit of detection. One of the advantages of cytogenetic dosimetry is that this biological dosimeter can be assessed at any moment, unlike physical dosimeters which are not always carried by a subject. Another advantage is that subjects under study cannot intentionally modify the biological dosimeter (6).

As reported earlier, different cytogenetic effects were observed in nuclear medicine workers. There are reports of significant increases in the level of chromosomal aberrations (3), in SCE frequencies, and in HFC (high frequency cells) percentages compared to control population (5).

The aim of this study was to provide data on the genetic hazards associated with occupational exposure to low doses of ionising radiation in Croatian nuclear medicine departments. Using the chromosome aberration analysis, we assessed the incidence of DNA damage in peripheral blood lymphocytes.

SUBJECTS AND METHODS

The population under study consisted of 120 volunteer blood donors: 60 were employees of nuclear medicine departments and 60 were unexposed control subjects. All participating subjects gave informed consent and were healthy at the moment of blood sampling and interviews. Blood samples were collected and further manipulated in accordance with high standards of ethics.

The exposed group included 37 women and 23 men employed in nuclear medicine departments of four Croatian hospitals and exposed to particulate emissions from different radionuclides (dominantly $^{131}$I and $^{99m}$Tc). The average age of the subjects was 42.5 years (range: 26 years to 59 years). All exposed subjects completed a standardised questionnaire including personal data, working activities, type and duration of occupational exposure at the time of the study, and information on exposure to possible confounding factors (smoking habit, alcohol use, medication intake, hormonal contraception, viral diseases, recent vaccinations, presence of known inherited genetic disorders, chronic disease, family history of cancer, exposure to indoor/outdoor pollutants, sunlight exposure, and radio diagnostic examinations). Twenty exposed subjects were smokers (12 women and 8 men), and 40 were non-smokers (25 women and 15 men). At the time of the study, the exposed subjects worked at nuclear medicine departments equipped and licensed for work with radionuclides, in compliance with national legislation. In their departments, all radiopharmaceuticals were prepared and dispensed in one place. Moreover, different radiation reduction measures and devices were also implemented. Mean duration of their occupational exposure at the time of blood sampling was 15.8 years (range: 1 year to 39 years). The exposed subjects were categorised in five subgroups according to their occupations: physicians (12 subjects: seven men and five women), technicians (26 subjects: 11 men and 15 women), engineers (eight subjects: five men and three women), nurses (seven women) and cleaners (7 women). During their work, all exposed subjects regularly wore personal dosimeters. Exposed technicians and nurses worked only in nuclear medicine departments and were not involved in other activities (e.g. working preparation and/or application of other drugs, including antineoplastic agents).

The control group consisted of 60 matched blood donors (37 women and 23 men). They were selected among healthy students and administrative staff. All of them came from the same geographical location, and their dietary habits were not appreciably different. The average age of the control subjects was 41.8 (range: 25 years to 59 years). Twenty controls were smokers (12 women and 8 men), while 40 were non-smokers (26 women and 14 men). At least one year before the study, the control subjects were not subjected diagnostic or therapeutic procedures using ionising or non-ionising radiation, nor did they have contact with whatever sources of ionising radiation. In addition no control reported a history of occupational exposure to known genotoxic chemicals or of alcohol.
abuse, medicine intake, inherited genetic disorders or chronic diseases for at least one year before the beginning of the study.

Peripheral blood samples were collected by venipuncture into heparinised tubes (BD vacutainer, Becton Dickinson, N.J., USA) on six different occasions over six months. Blood samples were always collected in the morning hours, between 9 and 10 a.m., on the last day of their workweek (a balanced collection design was used). Samples from both exposed and non-exposed individuals were handled in the same manner. After the collection, all blood samples were randomly coded, refrigerated at 4 °C, transported to the laboratory and processed.

The chromosome aberration test was performed in agreement with the current IPCH and IAEA guidelines (11, 12). Whole blood cultures were established by adding 0.5 mL heparinised whole blood into 5 mL of RPMI 1640 medium (Chromosome kit P, Euroclone) containing 10 % foetal bovine serum, phytohaemagglutinin, heparin, glutamine, growth factors, and antibiotic gentamycin. Duplicate cultures per subject were set up and incubated at (37±1) °C for 48 h. To arrest dividing lymphocytes in metaphase, colchicine (0.004 %) was added 2 h prior to the harvest. Cultures were centrifuged at 1000 rpm for 10 min, the supernatant was carefully removed, and the cells were resuspended in a hypotonic solution (0.075 mol L⁻¹ KCl) at 37 °C. After centrifugation for 5 min at 1000 rpm, the cells were fixed with a freshly prepared fixative of ice cold methanol / glacial acetic acid (3:1, v/v). Fixation and centrifugation were repeated several times until the supernatants were clear. Cells were pelleted and resuspended in a minimal amount of fresh fixative to obtain a homogeneous suspension. The cell suspension was dropped onto microscope slides and left to air-dry. Slides were stained with 5 % Giemsa solution (Sigma). All slides were coded and scored blindly. Metaphase analysis was conducted by a well-trained and experienced observer. Two hundred metaphases per subject (100 metaphases from each parallel culture) were analysed for chromosomal aberrations. Structural chromosome aberrations were classified based on the number of sister chromatids and breakage events involved. Only metaphases containing 45 to 47 centromeres were analysed. The evaluation included total number and types of aberrations, as well as the percentage of aberrant cells per subject.

We used Statistica 5.0 package (StatSoft, Tulsa, USA) for statistical analysis. Multiple comparisons between groups were made using multifactor ANOVA. Post-hoc analysis of differences was done using the Scheffé test. The level of statistical significance was set at p<0.05. The correlations between confounding factors and the parameters studied were also determined using the Pearson’s correlation matrices.

RESULTS

Figures 1 and 2 show individual chromosome aberration frequencies (CA) recorded in peripheral blood lymphocytes of occupationally exposed and control subjects. Table 1 reports group mean

![Graph](image-url)
frequencies of CA recorded among control and exposed subgroups. Mean frequencies of CA for the subgroups of exposed population are shown in Table 2.

In general, there was a statistically significant difference between the mean CA frequencies in the exposed medical personnel [(2.37±0.16) CA per 200 cells] and control subjects [(0.85±0.09) CA per 200 cells] (p<0.01, ANOVA). The total percentage of aberrant cells was also significantly higher in the exposed subjects (1.15±0.08) than in controls (0.23±0.06). The exposed subjects demonstrated noticeable inter-individual variations in aberration types. Control subjects, in contrast, had a more homogenous distribution of CA in their peripheral blood lymphocytes. An increased incidence of chromatid breaks was observed in the exposed subjects, with a mean frequency of (1.40±0.30) per 200 cells, while controls had (0.55±0.08) chromatid breaks per 200 cells. The mean frequency of chromosome breaks in the exposed subjects was (0.33±0.07) per 200 cells, while controls had (0.23±0.06).

Table 1 Incidence of structural chromosome aberrations (CA) in peripheral blood lymphocytes of nuclear medicine personnel and control subjects.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Σ</th>
<th>Σ CA</th>
<th>Cells with CA / %</th>
<th>Incidence of CA per 200 metaphases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chromatid break</td>
</tr>
<tr>
<td>NUCLEAR MEDICINE PERSONNEL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>37</td>
<td>2.41±0.21</td>
<td>1.16±0.10</td>
<td>1.41±0.17</td>
</tr>
<tr>
<td>Men</td>
<td>23</td>
<td>2.30±0.24</td>
<td>1.13±0.12</td>
<td>1.39±0.22</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>40</td>
<td>2.45±0.21</td>
<td>1.19±0.10</td>
<td>1.38±0.17</td>
</tr>
<tr>
<td>Smokers</td>
<td>20</td>
<td>2.20±0.21</td>
<td>1.08±0.11</td>
<td>1.45±0.22</td>
</tr>
<tr>
<td>Mean±SE</td>
<td></td>
<td>2.37±0.16</td>
<td>1.15±0.08</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.40±0.30</td>
<td>0.33±0.07</td>
<td>0.60±0.09</td>
</tr>
<tr>
<td>CONTROL GROUP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>37</td>
<td>0.81±0.11</td>
<td>0.39±0.06</td>
<td>0.54±0.09</td>
</tr>
<tr>
<td>Men</td>
<td>23</td>
<td>0.91±0.18</td>
<td>0.48±0.06</td>
<td>0.57±0.15</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>40</td>
<td>0.68±0.10</td>
<td>0.36±0.05</td>
<td>0.45±0.09</td>
</tr>
<tr>
<td>Smokers</td>
<td>20</td>
<td>1.20±0.19*</td>
<td>0.55±0.10</td>
<td>0.75±0.16</td>
</tr>
<tr>
<td>Mean±SE</td>
<td></td>
<td>0.85±0.09</td>
<td>0.43±0.05</td>
<td>0.55±0.08</td>
</tr>
</tbody>
</table>

† significantly increased compared to control subjects; * significantly increased compared to non-smokers; p<0.01 (multifactor ANOVA, post-hoc Scheffé test).
The mean yield of acentric fragments was \((0.60±0.09)\) per 200 cells in the exposed subjects and \((0.23±0.06)\) in controls. No dicentric chromosomes were found in the lymphocytes of control subjects. The mean yield of dicentric chromosomes in the exposed group was \((0.03±0.02)\) per 200 cells, that is, they were found only in two exposed technicians. The frequencies of chromosome aberrations were clearly elevated in all exposed subjects. All categories of aberrations were found, but without significant interaction between aberration type, sex, age and smoking habits. No statistically significant differences in the mean frequencies of chromosome aberrations were recorded between different occupations. Furthermore, no correlation was found between occupations, the time of exposure, whole-body radiation exposure, and the frequency of CA in individual cases. However, among controls there were significant differences in the total number of CA recorded between smokers \([1.20±0.19\) CA per 200 cells\)] and non-smokers \([0.68±0.10\) CA per 200 cells\)] (Table 1).

**DISCUSSION**

In this study we used a well-established biomarker of effect - chromosome aberration analysis - to evaluate the DNA damage in peripheral blood lymphocytes of nuclear medicine workers. As the results indicate, long-term occupational exposure to low doses of ionising radiation in nuclear medicine departments is associated with genotoxic effects. Nuclear medicine staff work almost exclusively with \(\gamma\)- and X-ray photons, ranging in energy from about 60 keV to 700 keV. This energy is sufficient to produce ionisation events and break molecular bonds. If this energy is deposited in the intracellular fluid, toxic compounds may be formed that can be detrimental to cell survival (damage by indirect action). A photon could also directly impact cellular DNA, causing strand breaks (damage by direct action.). At low doses, the body’s natural repair mechanisms usually perfectly repair any damage incurred (13). Many of induced DNA lesions are successfully repaired from a few minutes (4 min to 15 min) (14) to a couple of hours (2 h to 3 h) (15) after exposure. If the base damage is close between the opposite DNA strands (<10 bp apart), a simultaneous excision of such modified bases can lead to the formation of a double-strand break (DSB), which is believed to be the initial lesion in the formation of chromosome aberrations. Chromosome and chromatid breaks arise from DSBs that have been incompletely repaired or un repaired. The repair of DSBs can also produce double fragments, giving rise to polycentric chromosomes or centric ring chromosomes (16) which are visible on metaphase preparations.

Chromosome aberrations are a sensitive bioindicator reflecting individual radiation damage and radiosensitivity. In our study most chromosome aberrations detected in peripheral blood lymphocytes of the exposed and control population were of chromatid-type. Furthermore, nuclear medicine workers had a significantly higher incidence of chromosome breaks (over four times) than unexposed controls. These results are in good agreement with earlier observations, and point to the effects of radiation exposure. Similarly to the results reported by Hagelström et al. (3) our study showed

<table>
<thead>
<tr>
<th>Exposed subgroup</th>
<th>Dose per subject (\mu\text{Sv}/\text{ subject}^*)</th>
<th>(\Sigma) CA</th>
<th>Cells with CA / %</th>
<th>Incidence of CA per 200 metaphases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\Sigma)</td>
<td>Mean</td>
<td>Range</td>
<td>Chromatid break</td>
</tr>
<tr>
<td>Nurses</td>
<td>8</td>
<td>64</td>
<td>0-270</td>
<td>2.71±0.29</td>
</tr>
<tr>
<td>Engineers</td>
<td>7</td>
<td>149</td>
<td>0-360</td>
<td>2.50±0.53</td>
</tr>
<tr>
<td>Cleaners</td>
<td>7</td>
<td>217</td>
<td>0-1020</td>
<td>2.43±0.43</td>
</tr>
<tr>
<td>Technologists</td>
<td>26</td>
<td>305</td>
<td>0-1401</td>
<td>2.27±0.26</td>
</tr>
<tr>
<td>Physicians</td>
<td>12</td>
<td>56</td>
<td>0-500</td>
<td>2.25±0.35</td>
</tr>
<tr>
<td>Mean±SE</td>
<td></td>
<td></td>
<td></td>
<td>2.37±0.16</td>
</tr>
</tbody>
</table>

* effective dose recorded on personal dosimeter one month prior to the study

(0.07±0.03) chromosome breaks per 200 cells. The mean yield of acentric fragments was \((0.60±0.09)\) per 200 cells in the exposed subjects and \((0.23±0.06)\) in controls. No dicentric chromosomes were found in the lymphocytes of control subjects. The mean yield of dicentric chromosomes in the exposed group was \((0.03±0.02)\) per 200 cells, that is, they were found only in two exposed technicians. The frequencies of chromosome aberrations were clearly elevated in all exposed subjects. All categories of aberrations were found, but without significant interaction between aberration type, sex, age and smoking habits. No statistically significant differences in the mean frequencies of chromosome aberrations were recorded between different occupations. Furthermore, no correlation was found between occupations, the time of exposure, whole-body radiation exposure, and the frequency of CA in individual cases. However, among controls there were significant differences in the total number of CA recorded between smokers \([1.20±0.19\) CA per 200 cells\)] and non-smokers \([0.68±0.10\) CA per 200 cells\)] (Table 1).
that a radiation worker exceeds this dose. With current regulatory safeguards in place, it is rare for a dose-effect relationship for low doses of radiation to be observed (3, 9). Low yields of dicentrics and no rings were found only in two exposed subjects. It is important to note that dicentrics and ring figures are unstable chromosome aberrations generally observed as the consequence of an in vitro or an acute in vivo ionising irradiation (22). Low yields of dicentrics and no rings recorded in our study were probably due to the low level of occupational radiation exposure. It is also possible that most exposed subjects in our study followed the radiation safety guidelines and used protective devices at work. Long-term occupational exposure to radiation is related to the induction of stable balanced translocations in peripheral blood lymphocytes (17). However, this possibility has to be studied on the same population in future using the chromosome painting techniques.

The exposed population demonstrated great inter-individual heterogeneity in DNA damage, especially where there was no relationship between the extent of exposure, doses received and the levels of DNA damage recorded. This observation raises the general question of the relationship between the induction of DNA damage in resting lymphocytes, and its subsequent fixation in genetic alterations after stimulation. We assume that most DNA damage induced in vivo in circulating lymphocytes is repaired, thus escaping fixation, as was also reported in other studies (18, 19).

Heterogeneity in DNA damage recorded in the exposed subjects could also be attributed to other confounding factors including specific modes of exposure, different radiation doses received, differences in individual genome sensitivity, various lifestyle-associated factors, as well as to compliance with radiation safety guidelines during everyday work. Because specialised workers often tend to perform the same tasks, it is quite possible that some of them would sustain higher levels of DNA damage. Therefore, it is likely that subjects with high levels of DNA damage were involved in specific procedures associated with higher exposure.

In our study, DNA damage recorded was not in positive correlation with the effective dose recorded. Other authors also argue that it is difficult to establish a dose-effect relationship for low doses of radiation (20, 21). Today, the recommended maximum annual occupational dose limit is 50 mSv (10, 13). However, with current regulatory safeguards in place, it is rare that a radiation worker exceeds this dose.

For X- or γ-rays, good evidence of an increase in risk for cancer is shown at acute doses >50 mSv and reasonable evidence is given of an increase in some cancer risks at subacute doses above 5 mSv (22). At doses much higher than 0.5 Gy, radiation exposure is clearly a known carcinogen, primarily due to its mutagenic effects on cells. However, it is difficult to say that any cancer is solely caused by radiation exposure, as cancer may be caused by a combination of factors (23). Given our current state of knowledge, the most reasonable assumption is that the cancer risks from low doses of X- or γ-rays decrease with dose (22). Doses recorded among the exposed subjects one year before our study began (data not shown) were well below the maximum annual occupational dose limit. One month before blood sampling, these doses were mostly in the range of μSv, not mSv.

Generally speaking, exposure to ionising radiation may produce both deterministic and stochastic effects. Radiation workers run greater risk of deterministic effects only if they fail to observe hospital safety policies and procedures. Cancer and genetic mutations are the examples of stochastic effects caused by occupational exposure to ionising radiation. These are long term effects, which do not show in the exposed population until many years after the exposure. The exact risk of radiation-induced cancer at very low doses is not totally understood and is further complicated by many factors, such as the magnitude of the dose, the time span over which the dose was delivered, the general state of the health of the individual, the type of radiation to which the individual was exposed, the energy of the radiation and the area of the body to which the dose was delivered, among others (13).

In conclusion, it is important to realise that radiation exposure, environmental or occupational alike, is not the only risk factor in our lives, nor is it the most prominent. Our study indicates the possibility of genotoxic implications in nuclear medicine personnel occupationally exposed to low doses of ionising radiation for an extended period. To avoid possible genotoxic effects, the exposed medical personnel should carefully apply radiation protection procedures and should minimize occupational radiation exposure. Our results also confirm that chromosome aberrations are important biological indicators and sensitive predictors of the actual risk run by radiation-exposed individuals. This is especially true for the distribution and the extent of radiation exposure, as these data are seldom provided by physical dosimetry.
Acknowledgement

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REFERENCES


Sažetak

PROCJENA CITOGENETIČKIH OŠTEĆENJA U MEDICINSKOG OSOBLJA PROFESIONALNO IZLOŽENOG NISKIM DOZAMA IONIZIRAJUĆEG ZRAĆENJA NA ODJELIMA NUKLEARNE MEDICINE

Ionizirajuće zračenje izaziva različita oštećenja u živim stanicama, čija je pojava ovisna o dozi kojoj su stanice izložene, apsorbiranoj dozi, trajanju izloženosti te osjetljivosti tkiva. Osoblje profesionalno izloženo zračenju pod povećanim je rizikom od štetnih učinaka ionizirajućeg zračenja samo u slučajevima nepoštivanja propisa sigurnosti pri radu. Dugogodišnja profesionalna izloženost zračenju za posljedicu može imati zločudne bolesti (rak) i genske mutacije. Unatoč intenzivnim istraživanjima, genetska oštećenja proizašla iz izloženosti osoblja ionizirajućem zračenju još nisu potpuno razjašnjena, a posebice ona proizašla iz izloženosti niskim dozama. Cilj ovog istraživanja bio je proučiti genetska oštećenja nastala pod utjecajem profesionalne izloženosti niskim dozama ionizirajućeg zračenja u osoblja zaposlenog na odjelima nuklearne medicine. Procjena oštećenja DNA u limfocitima periferne krvi izloženoga medicinskog osoblja provedena je s pomoću testa analize kromosomskih aberacija. Istraživanje je obuhvatilo ukupno 120 ispitanika (60 izloženih i 60 kontrolnih). U izloženih ispitanika utvrđena je statistički značajno povišena učestalost kromosomskih aberacija u usporedbi s kontrolnom skupinom. Unutar izložene skupine uočene su i značajne interindividualne razlike u razini oštećenja DNA, koje upućuju na različitu genetsku osjetljivost. Dob i spol ispitanika nisu značajnije utjecali na razinu oštećenja DNA samo u ispitanika kontrolne skupine. Na osnovi dobivenih rezultata vidljivo je da kronična profesionalna izloženost niskim dozama ionizirajućeg zračenja na odjelima nuklearne medicine izaziva genetotskična oštećenja u limfocitima periferne krvi medicinskog osoblja. Kako bi se izbjegli potencijalni genetotskični učinci, izloženost medicinskog osoblja, kad god je to moguće, treba smanjiti na najmanju moguću razinu. Dobiveni rezultati također naglašavaju važnost primjene bioloških indikatora koji pružaju niz informacija o stvarnom i trenutačnom riziku za izložene ispitanike koji se ne mogu dobiti iz fizikalne dozimetrije.

KLJUČNE RIJEČI: kromosomske aberacije, limfociti periferne krvi, oštećenja DNA, radioizotopi, rizik

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