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Chromosomal Aberrations, Micronuclei, Blood Parameters and Received Doses in Workers Exposed to Ionizing Radiation

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Abstract

Background: *This study aimed to analyze the impact of low doses of ionizing radiation on healthcare workers using dosimeter data and several biomarkers of effects and to assess the suitability of those tests.* **Methods:** *Data from the last medical examinations, obtained from the medical records of 148 healthcare workers, were analyzed. They were divided into three groups of workers: nuclear medicine (NM), interventional radiology (IR), and general radiology (GR). The examination included hematological parameters and cytogenetic tests: unstable chromosomal aberrations (UCAs) and micronucleus test (MNT). The received cumulative 5-year dose was calibrated into personal dose equivalents Hp (10)(PDE).* **Results:** *There were older employees and more women in NM than in the other two groups. NM workers had more years of exposition than employees in IR and GR. PDE and years of exposition were significantly higher in NM. In the multivariate logistic regression model NM group was positively related to UCAs after adjusting for age, sex, and smoking. According to the results of the multivariate analysis, female healthcare workers and those employed at IR had higher values of erythrocytes than males and those employed in NM or GR departments.* **Conclusions:** *Nuclear medicine workers are at a higher risk of developing neoplastic due to consistent exposure to low doses of ionizing radiation. The results indicate that the UCAs test might be more suitable for detecting radiation-induced damage at low doses than MNT. Compulsory monitoring of the health status at periodic examinations is required to prevent occupational diseases of nuclear medicine workers.*

1. Introduction

Ionizing radiation, often used in medicine, can cause adverse medical conditions when safety procedures are not followed [1, 2]. Radiation toxicity depends on the type of radiation emissions and characteristics of the tissue itself [2, 3-5]. Occupational diseases, including occupational carcinoma, are higher in more sensitive organs. Levels of radiation emissions are regulated in the Rulebook on determining occupational diseases [6].

Mature lymphocytes, taken from peripheral blood, had been used for bio-dosimetry testing, essential in radiological protection and occupational medicine. These assays include unstable chromosomal aberrations (UCAs) and the micronucleus

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test (MNT). UCAs in peripheral blood lymphocytes have been recognized as biomarkers of the effect of ionizing radiation. MNT has been used as a screening method to demonstrate the cytoplasm's aberrant chromosomal material (micronuclei) [7]. Both tests are significant indicators for identifying an occupational disease, such as cancer, caused by small doses of ionizing radiation in the workplace over a few years [1, 2, 8-13].

Unstable chromosomal aberrations include different types, such as acentric, dicentric, and ring chromosomes, as well as unspecific damages [8, 13]. The frequency of the UCAs and the number of micronuclei (MN) is higher in people exposed to acute irradiation, and a significant correlation has been identified with the dose received. Also, frequencies depend on the radionuclide metabolism and the patient's health condition [9, 14, 15].

It has been proven that nuclear workers have an increased risk of cancer, recognized as an occupational disease, due to the increased frequency of unstable chromosomal aberrations and the number of micronuclei [15]. The hematopoietic system is the most sensitive, reticulocytes (as descendants of erythroblast) and leukocytes [1, 16]. In Serbia, the effects of occupational exposure to ionizing radiation have to be assessed with regular preventive-periodical medical examinations.

Certain areas of medicine, such as nuclear medicine, interventional radiology, and general radiology, use ionizing radiation for diagnostic and therapeutic purposes, and the employees are occupationally exposed to relatively low doses. According to the Rulebook on Limits of Exposure to Ionizing Radiation and Measurements for Assessment of the Exposure Levels [17] for occupationally exposed persons, permissible yearly effective doses range from 6 mSv to 20 mSv [1]. Previous or initial examination and periodical check-ups are compulsory in Serbia, and this is regulated in the Rulebook on the Preliminary and Periodical Medical Examinations of Workers with Elevated Health Risk at their workplaces [18]. The check-ups include the hematological parameters and specific cytogenetic tests (UCAs and MNT) following the law [19].

The purpose of this study was to compare the influence of low doses of ionizing radiation on exposed medical workers in nuclear medicine, interventional radiology, and general radiology. Also, different settings were applied through analysis of UCAs, MNT, hematological parameters, and the cumulative 5-year dose. These groups were chosen according to the source and type of ionizing radiation: nuclear medicine employees have been exposed to alpha, beta, and gamma radiation from open sources, while interventional and general radiologists have been exposed to X-rays only (closed sources, only emitting while the devices were energized).

2. Methods

The data for this study had been collected during the last preventive periodical medical examinations in the Serbian Institute of Occupational Health following the Law on Radiation Protection and Nuclear Safety and Security [19]. Analyzes have been done following the ethical principles of the Declaration of Helsinki and the principles of the Ethics Committee of the Faculty of Medicine, University of Belgrade. Information was obtained from the medical records of 148 healthcare workers exposed to ionizing radiation at the University Clinical Centre of Serbia.

The UCAs were obtained by the modified Moorhead's micro method [20]. For this analysis, 0.1 ml of heparinized peripheral vein blood lymphocytes were treated with 0.1 % phytohemagglutinin (PHA) and left aside at 37 °C for mitosis stimulation. After 45 hours, this culture was treated with colchicine to stop mitosis when the chromosomes were most visible in the metaphase. Then, after 2 hours of sample preparation, UCAs were measured. The positive results for workability are if more than one dicentric per 200 metaphases lymphocytes, one or more ring chromosomes per 200 metaphases lymphocytes, and more than two entries per 200 metaphases lymphocytes [21, 22].

The micronucleus test was performed using the Fenech and Morley method [23, 24]. Peripheral blood lymphocytes were used to observe the micronuclei. After 45 hours of cell cultivation, cytochalasin-B, an actin inhibitor, was added to block the cytokinesis and facilitate the karyokinesis (a division of the nucleus only). After 72 hours from the beginning of the test, a binuclear lymphocyte with a certain number of micronuclei in the cytoplasm was obtained. The test result was positive if it included 25 or more micronuclei, according to the reference values adopted by the Laboratory for Cytogenetics at the Serbian Institute of Occupational Health.

The hematological samples (erythrocytes, reticulocytes, total leukocytes, lymphocytes, monocytes, neutrophils, eosinophils, and platelets) were collected by processing the peripheral vein blood using a Beckman Coulter HMX system. The absolute values of cell counts (reticulocytes, monocytes, neutrophils, and eosinophils) were considered. To reduce the confounding effects, the subjects also had to fill out a compulsory questionnaire containing information on smoking habits, anti-neoplastic drugs, recent viral diseases, and possible exposure to chemical solvents, pesticides, and ionizing radiation for diagnostic purposes in the last six months. All these factors were used as the exclusion criteria in this study, except for the smoking habits, especially having difficulties collecting adequate information in mind.

Data on the received cumulative 5-year doses have been obtained using personal dosimeters (TLDs), calibrated in terms of the personal dose equivalent Hp(10) using the Harshaw TLD 6600 Reader. The comparisons were made between healthcare workers in three work areas (nuclear medicine, interventional radiology, and general radiology) in the frequency of UCAs, MNT results, hematological parameters, and cumulative 5-year received dose (5-year PDE) measured during the work shift.

Data were processed using the IBM SPSS 20 package for Windows. The analyses included the Chi-square test, Fisher test, One-Factor Analyses of Variance (ANOVA), Sidak Multiple Comparisons test, Kruskal–Wallis test, and Mann-Whitney test.

The univariate and multivariate linear regression analysis was used to determine factors related to hematological parameters adjusted on age, sex, and smoking status. The univariate and multivariate logistic regressions were used to determine the independent predictors for UCA and MNT adjusted on age, sex, and smoking status. Results are expressed as linear regression coefficients (B) or the odd ratios (OR) where appropriate and their 95% confidence intervals (CI). All tests were two-tailed. Statistically significant was considered as of $p< 0.05$.

3. Results

The study comprised 148 subjects, including 104 females (55 in nuclear medicine, 25 in interventional radiology, 26 in general radiology) and 44 males (8 in nuclear medicine, 22 in interventional radiology, 11 in general radiology) of average age 45.73±11.59 yrs, with the average total work experience 19.43±10.9 yrs (39 at most) and average 15.37±9.36 yrs (35 at most) of exposure.

The subjects were divided into three groups based on their area of work. There were 65 (43.9 %) workers in nuclear medicine, 47 (31.8 %) in interventional radiology, and 36 (24.3 %) in general medicine. The

Table 1. Different predictors and work area.

Variables	Interventional radiology	Nuclear medicine	General radiology	P
Age	38.7+9.8	51.9+11.2	43.6±8.4	**p<0,001**
Sex	22/47 male	8/64 male	11/37 male	**p<0,001**
	25/47 female	56/64 female	26/37 female	
Smoking	20/47 no	27/64 no	18/37 no	p>0,05
	27/47 yes	37/64 yes	19/37 yes	
EWP (yrs)	9 (0-32)	18.5 (0-35)	15 (3-31)	**p=0.002**
5-year PDE (mSv)*	5.6 (3.1-25.11)	8.9 (2.33-44.35)	4.3 (3.62-41.26)	**p<0.001**

**The effective dose of occupationally exposed persons is: very high if it is greater than 50 mSv in a year; high if it is greater than 20 mSv in a year; increased if it is more significant than six mSv in a year; low if it is less than or equal to 6 mSv for a year; very low if it is less than or equal to 2 mSv in a year; negligible if it is less than or equal to 1 mSv for a year.*

difference between these three groups according to the different predictors is presented in Table 1.

According to the predictors such as age, sex, smoking, exposure work period (EWP), and received cumulative dose for 5 years (personal dose equivalent/ PDE), examined predictors differed significantly between groups. A statistical significance was found in the age, sex, exposure work period, and the received 5 years dose.

One-Factor Analysis of Variance (ANOVA) was conducted to analyze the effect of the group according to age. The significance was detected ($F_{(2,143)}$=9.220, p<0.001, Partial Eta Squared=0.050). There were much older employees in nuclear medicine than in other two groups. More women were employed in nuclear medicine (Chi-squared test, χ^2= 16,027; p<0.001).

Nuclear medicine workers had more years of exposition than employees in interventional and general radiology (Kruskal-Wallis test (χ^2=12,276; p=0.002).).

The five-year cumulative doses, calibrated in personal dose equivalents Hp (10) (5-year PDE), presented in the Table 1, exhibited a statistically significant difference among the three groups using the Kruskal-Wallis test (χ^2=22,191; p< 0.001). A statistically significant difference was found between the nuclear medicine group and the interventional radiology group (Mann-Whitney U=458, p<0.001). The difference between the nuclear medicine and general radiology was also highly statistically significant (Mann-Whitney U=510.5, p<0.001), while there was no statistically significant difference between interventional radiology and general radiology (Mann-Whitney U=604, p=0.294). The results of the UCAs test, from the last periodic examination, are presented in the Table 2.

The MNT results, from the same examination are presented in the Table 3.

One-Factor Analysis of Variance (ANOVA) was conducted to analyze the effect of group and gender on the erythrocyte count. The results showed a statistically significant difference in the values of erythrocytes between employees in the three groups ($F_{(2,140)}$=3.715, p=0.027, Partial Eta Squared=0.050).

Multiple comparisons were performed using the Sidak test. A significantly higher erythrocyte count was detected in the interventional radiology group compared to general radiology (p=0.009) and compared to nuclear medicine (p<0.001). Other hematological parameters (reticulocytes, leukocytes, neutrophils, monocytes, eosinophils, lymphocytes,

Table 2. Frequency of the unstable chromosomal aberrations (UCAs) in the occupationally exposed employees in different areas of work.

Work area	Normal frequency N [%]	Higher frequency N [%]	Total N [%]
Nuclear medicine	49 (84.5)	9 (15.5)	58 (100.0)
Interventional radiology	27 (96.4)	1 (3.6)	28 (100.0)
General radiology	26 (100.0)	0 (0.0)	26 (100.0)
Total	**102 (91.1)**	**10 (8.9)**	**112 (100.0)**

Table 3. The outcome of the micronucleus test at the last periodical examination in occupationally exposed employees in different areas of work.

Work area	Normal number of micronuclei N [%]	Elevated number of micronuclei N [%]	Total N [%]
Nuclear medicine	46 (83.6)	9 (16.4)	55 (100.0)
Interventional radiology	19 (76.0)	6 (24.0)	25 (100.0)
General radiology	27 (87.1)	4 (12.9)	31 (100.0)
Total	**92 (82.9)**	**19 (17.1)**	**111 (100.0)**

Table 4. Multivariate regression model of variables associated with UCAs.

Variables	OR (95 % CI)	*p* value
Age	0.97 (0.88-1.06)	0.459
Sex	0.28 (0.04-1.74)	0.897
Smoking	0.29 (0.06-1.48)	0.295
Cumulative doses	1.03 (0.93-1.15)	0.545
Nuclear Medicine	21.02 (1.65-268.07)	**0.019**

Table 5. Multivariate regression model of variables associated with RBC.

Variables	B (95% CI)	*p* value
Age	0.002 (-0.005-0.009)	0.533
Sex	-0.53 (-0.69 to -0.38)	**<0.001**
Smoking	0.08 (0.64-1.08)	0.232
Cumulative doses	0.59 (-0.05-0.21)	0.793
Interventional radiology	0.19 (0.02-0.35)	**0.024**

platelets) did not show significant differences between the groups ($p>0.1$).

In the multivariate logistic regression model nuclear medicine group ($p=0.019$) was positively related to UCAs after adjusting for age, sex and smoking (Table 4).

Workers employed at nuclear medicine department had higher risk for elevated UCAs compared to workers employed at interventional radiology or general radiology. According to the results of the multivariate analysis, factors associated with values of erythrocytes were sex and interventional radiology group after adjusting for age and smoking (Table 5).

Female healthcare workers and those employed at interventional radiology had higher values of erythrocytes than males and those employed at nuclear medicine or general radiology departments.

4. Discussion

Based on the available literature, it is generally agreed that ionizing radiation can affect various health parameters and cause carcinogenesis. The biological effects of small doses on human health have been debated for many years. Still, the literature on their impacts on workers' health in different work settings, especially in healthcare, is scarce [11, 12, 14, 25, 26]. It was noted that prolonged exposure to radiation in the workplace increases the risk of developing cancer in cardiac catheterization laboratory staff with the highest exposure levels [27].

Differences in response to radiation (chromosome aberrations) between radiation-sensitive and radiation-resistant individuals should be considered in the risk assessment from radiation exposure [28]. A study on nuclear power plant workers in South Korea demonstrated that chromosomal damage could be induced in individuals exposed to doses below the occupationally permissible limits [29].

To observe the effects of low doses of ionizing radiation, UCAs and MN as biomarkers of the effect are important not only for the assessment of work ability but also for the assessment of radiation risks due to stochastic-cumulative effects that do not directly depend on the dose [3, 14, 25]. A review of the effects on healthcare workers exposed to low doses of ionizing radiation confirms the relevance of UCAs and MN, which are consistently increased in radiation-exposed workers compared to unexposed [30]. In one study, nuclear medicine workers were associated with higher received doses and an increased frequency of UCAs [14]. The frequency of UCAs cumulates with the received dose (X-ray and Gamma radiation) [3, 14], and in one study, a six-year cumulative effect of the received dose was observed [31].

Our study found a significant difference between the UCAs among the three groups, where the nuclear medicine group had a much larger proportion of positive UCA tests after adjusting for age, sex, and smoking. This implies a higher risk of cancer among nuclear medicine workers, requiring strict exposure, health monitoring, and adherence to all the safety protocols.

The MNT is considered important in the bio-dosimetry of employees in nuclear medicine because of an elevated risk of internal radiation contamination [7]. It represents chromosomal instability and can also indicate chromosomal damage induced by radiation [32]. This test is also suitable for rapid automated detection of chromosomal damage [33].

One study found that the MNT is generally comparable in sensitivity to the chromosomal aberrations test [34]. Another study suggests the usefulness of the MN test for detecting the effects of low cumulative ionizing radiation doses in medical screening programs [35]. A recent study concluded that chromosomal aberrations (dicentrics) are more typical for exposure to radiation than micronuclei [36].

In our study, no statistically significant difference was found in the outcome of the MNT between the three groups. Since we found a significantly higher received dose Hp (10) in the nuclear medicine group, compared to the other two groups, the MNT may not be suitable as the UCA test for detecting genetic damage due to small received doses of ionizing radiation. In assessing this damage, it would be advisable to perform both tests wherever possible.

The specific positive findings, such as UCAs, can be explained by the specific risk of workplace exposure to radio-nuclides with higher radiobiological effects (a, b and γ emitters).

Hematological parameters react to the received dose, especially the number of leukocytes and lymphocytes. Studies on experimental animals and the exposed human population show that the hematopoietic system responds to acute high-dose irradiation and to repeated lower irradiation doses of the whole body [37]. However, monitoring the effect of exposure to small doses is very difficult.

In a study of hematological parameters in the hospital staff chronically exposed to low doses of ionizing radiation, a decrease in the value of most hematological parameters was observed, with a statistically significant difference in comparison to unexposed workers found in the mean corpuscular hemoglobin and lymphocyte count [37]. The authors conclude that exposure to doses lower than 20 mSv could affect the immune system's quality and contribute to anemia.

In our study, female healthcare workers and those employed in interventional radiology had higher values of erythrocytes than males and those employed in nuclear medicine or general radiology departments. This finding is unspecific and cannot be explained by the influence of ionizing radiation. In interpreting hematological findings, attention had been required because of many non-radiation-related factors that can impact the results. An exact dose-response relationship in the hematological parameters at low exposed radiation doses on analyzed subjects had not been detected. In contrast, the cytogenetic tests did follow an increasing dose-response trend, which barely reached statistical significance in the UCA test. The cytogenetic tests are more specific for radiation-induced damage than hematological parameters and therefore offer a more reliable insight in cases of exposure to low radiation doses.

5. Conclusions

The most radiation-exposed group consisted of employees in the area of nuclear medicine. In the presented study, this exposure was associated with slightly higher UCA frequency which is still good for assessment of work ability. This, in turn, causes a higher risk of cancer occurrence in the future. Results of this study suggest that the UCA test might be more suitable than MNT for detecting low ionizing radiation impacts on employees' health.

Employees exposed to low doses of ionizing radiation are at a higher risk of developing neoplastic and blood-related diseases. Out of all three groups of subjects (nuclear medicine, interventional radiology, and general radiology), employees in nuclear medicine are at special risk due to different types of exposure (work with radio-nuclides).

Mandatory health status monitoring at periodic examinations and adequate safety at work is required to prevent occupational diseases.

Institutional Review Board Statement: This study involves human participants and was approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade (No 440/X-10).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study

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