JBUON 2016; 21(5): 1307-1315
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Analysis of chromosomal aberrations frequency, haematological parameters and received doses by nuclear medicine professionals

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Summary

Purpose: *The purpose of this article was to analyse the impact of low-dose ionizing radiation to nuclear medicine professionals of the Nuclear Medicine Centre of Serbia (NMCRS).*

Methods: *Data from the previous/initial and the last medical check-ups, obtained from the medical records of 65 employees from NMCRS, were analysed. A typical check-up, haematological parameters analysis, as well as special cytogenetical analyses, such as unstable chromosomal aberrations and micronucleus test, were carried out. For analyses of chromosomal aberrations the modified Moorhead's micro method was applied to the culture of peripheral blood lymphocytes and conventional cytogenetic technique of chromosomal aberrations was applied. The received cumulative 5-year dose was measured by personal inactive thermoluminescent dosimeters (TLD) calibrated into personal doses equivalent Hp(10).*

Results: *An increased frequency of all unstable chromosomal aberration forms, such as acentric chromosomes and isochromatid lesions, was noticed in the last periodical check-up as compared to the previous/initial check-ups ($p<0.05$). As for haematological parameters, a higher erythrocytes and monocytes count in the periodical check-ups was noticed ($p<0.01$). There was a negative correlation between reticulocytes and received 5-year cumulative dose ($p<0.01$). The duration of exposure had significant influence on higher level of leucocytes in the last periodical check-up ($p<0.05$).*

Conclusions: *Nuclear medicine employees have increased health risks and there is a need to monitor their health condition by periodical check-ups for prevention from occupational diseases (carcinoma).*

Key words: *chromosomal aberrations, cumulative dose, occupational medicine.*

Introduction

Ionizing radiation is often used in medicine for diagnostic and therapeutic purposes [1]. Radiation workers exposed to ionizing radiation have to follow all the safety measures and precautions at their work. Should all safety procedures not be followed, human health may be seriously endangered by ionizing radiation [1,2]. Nuclear medicine workers, are occupationally exposed to low-doses of ionizing radiation (for those who are occupationally exposed, effective doses range from 6 to 20 mSv, according to the Rulebook on Limits of Exposure to Ionizing Radiation and Measurements for Assessment of the Exposure Levels - Official Gazette RS 86/11 from November 18, 2011) [3].

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Received : 24/03/2016; Accepted : 11/04/2016

Nuclear medicine workers can be exposed to ionizing radiation during radioactive materials manipulation. This usually occurs after application of radiopharmaceuticals and during the interaction with irradiated patients. Occupationally exposed to radiation in the nuclear medicine are: nuclear medicine specialists, lab technicians, radiologists, physicists, and engineers. Despite of being exposed to low doses there is still a risk of health influence, especially to the genetic material, and it may also result to occupational carcinoma [1,2,4-7].

Both risks and advantages of ionizing radiation during medical procedures (nuclear medicine, interventional radiology and general radiology) must be explained and clearly stated to each party – patients as well as the physicians. The main rule in the radiation protection is based on ALARA principle (as Low as Reasonably Achievable).

Radiotoxicity depends on the type of radioemission and characteristics of the tissue itself [2,8-13]. The appearance of occupational diseases, including occupational carcinoma, is higher if the organ is more sensitive (which is all stated in the Rulebook on determining occupational diseases) [14].

The most sensitive immature blood cells are erythroblasts. The mature ones are lymphocytes, and are taken from peripheral blood for biodosimetry test purposes – important for the field of radiological protection in the occupational medicine (unstable chromosomal aberrations - UChAs and micronucleus test). The unstable chromosomal aberrations of peripheral blood lymphocytes have been recognized as biomarkers of the effect of ionizing radiation. They are also very important for health risk evaluation and occupational carcinoma diagnosis [2,15-18].

Forms of the unstable chromosomal aberrations are acentric, dicentric and ring chromosomes, as well as unspecific lesions of unspecific damages [4,17,19]. The frequency of the unstable chromosomal aberrations is higher in people exposed to acute irradiation and there is also a significant correlation with the dose received. Also, it depends on the radionuclide metabolism and patient's health condition [7,20,21].

The effects on radiosensitive organs are important as well – the most sensitive of all is the haematopoietic system, i.e. leukocytes and reticulocytes as descendants of erythroblast. Observation of the effect of occupational exposure to ionizing radiation is done within the preventive-periodical medical examinations.

Previous or initial and periodical check-ups are compulsory and their elements are given in the Rulebook on the preliminary and periodical medical examinations of workers with increased risk at their workplaces (Official Gazette of the Republic of Serbia No120/07) [22].

One of the elements of the examination is analysis of the haematological parameters. Regarding the previous/initial medical examinations, specific cytogenetic analyses had been obligatory (analyses of the unstable chromosomal aberrations and micronucleus test), and, according to the new Rulebook [3] concerning the periodical medical examination, only the micronucleus test is mandatory. Preventive periodical medical examinations had been done in the Serbian Institute of Occupational Health in accordance with the Law on Radiation Protection and Nuclear Safety [23].

The purpose of this study was to estimate the influence of ionizing radiation on nuclear medicine employees through analysis of chromosomal aberrations frequency, validity of haematological parameters (influence of the received dose), and the length of exposure to ionizing radiation (exposed work period).

Methods

Information was obtained from the medical records of the 65 workers at the Nuclear Medicine Centre of the Clinical Centre of Serbia, and was analysed in accordance with the ethical principles of the Helsinki Declaration and the principles of the Ethical Committee of the School of Medicine in Belgrade. Data were taken from the previous/initial check-ups, which had been done before the entrance to the zone of ionizing radiation, or during the first year of exposure to radiation (during the specialization period, in accordance with employer's decision to send an employee to the examination) and from the last periodical examination.

Unstable chromosomal aberrations were obtained by the modified Moorhead's micro method. For this analysis 0.1 ml of heparinized peripheral vein blood was taken and treated with 0.1% phytohemagglutinin and then left aside at 37 °C for 48 hrs for mitosis stimulation. Afterward, this culture was treated by colchicine after 45 hrs to stop mitosis in metaphase, when the chromosomes are most visible [24].

To prevent false positive and false negative results, those who were tested also had to fill in a compulsory questionnaire, which was then analyzed. The questionnaire contained information on smoking habits, medications, recent viral diseases, possible exposure to chemical solvents, pesticides and ionizing radiation for diagnostic purposes. There were no restrictions about smoking habits. The haematological parameters (erythrocytes, reticulocytes, total leucocytes, monocytes, neutrophils, eosinophils, basophils and platelets) were gathered by processing the peripheral vein blood by Beckman Coulter HMX (at the periodical check-ups), but mostly by the old method of manual cell counting (at the previous/initial check-ups). The absolute values were taken into consideration (reticulocytes, monocytes, neutrophils, eosinophils and basophils).

Data on the received cumulative 5-year doses were obtained by using personal TLDs, calibrated in terms of the personal dose equivalent Hp(10) (PDE) on the Harhaw TLD 6600 Reader (calibrated dosimeters were irradiated in the Laboratory for Calibration of the Vinca Institute of Nuclear Sciences).

The analysis referred to two aspects: difference in the frequency of the unstable chromosomal aberrations and values of the haematological parameters of the periodical check-up as compared to the previous/initial check-ups. The comparison was made between the frequency of unstable chromosomal aberrations with the haematological parameters in the last periodical check-up and cumulative 5-year received dose (5-year PDE). Later, the relationship of haematological parameters in the last periodical check-up and cumulative 5-year received dose was also compared. Furthermore, the influence of the exposed working period (EWP) on the frequency of the unstable chromosomal aberrations for 5-year period (5 year PDE), and haematological parameter values at the last periodical check-up were also taken into consideration.

Statistics

Data were statistically processed using the SPSS Statistical Program version 16 for Windows. The numbers were obtained by measuring the central tendency (arithmetic mean), and variability (variation interval, standard deviation). Student's t-test was used for connected and unconnected samples, Mc Nemar's test for paired nominal data, Wilcoxon's Signed Rank test for comparing two related samples and Pearson's linear correlation coefficient for linear correlation between two variables.

A p value < 0.05 was considered as statistically significant.

Results

This study included 65 examinees of which 57 were females and 8 males, with average age of 51.46 ± 11.3 years.

At the previous/initial examination, among 38 examinees for the unstable chromosomal aberrations, 34 (89.5%) did not have increased frequency of chromosomal aberrations, while 4 (1.5%) showed increased frequency.

According to the results of the periodical check-up, among 58 examinees who had undergone cytogenetical investigations, 9 (15.6%) had increased frequency while 49 (74.4%) had not. The correlation between those who had and those who had not increased frequency of chromosomal aberrations at the previous/initial and periodical examinations is presented in Table 1.

Table 2 displays the frequency of the various forms of the unstable chromosomal aberrations at the previous/initial and periodical medical examinations. Statistically there was no significant difference regarding the frequency of dicentric chromosomes as shown by the Mc Nemar's test (p=0.453). Comparison of the ring chromosome and chromatid lesions gave the same results. At the initial check-up there was only one case of ring chromosome, and the same result appeared at the periodical check-up, meaning that there was no statistical significant difference – as shown by Mc Nemar's test (p=1.000).

Both examinations included 30 people who were subjected to cytogenetic tests; 21 of them did not have chromatid lesions, while 5 had one lesion and 4 had two. (Wilcoxon's Signed Rank test, p=0.183). Both examinations showed that, as far as the frequency of the acentric chromosomes is concerned, 14 people did not have acentrics at the initial check-up, 3 had only 1, while one person had 2 acentrics. However, at the periodical check-up 10 people had one acentric, 3 had 2, while one had 3 acentric chromosomes. The quoted examinations illustrate the statistical importance between the frequencies of the acentric chromosomes by Wilcoxon's Rank test (p=0.025; Table 3).

Table 1. Frequency of unstable chromosomal aberarrations (fUChA) at the previous/initial and periodical medical examination

		fUChA on very first check up		*Total*
		Normal frequency N (%)	*Higher Frequency N (%)*	
fUChA on periodical check-up	No	24 (80.0)	6 (20.0)	30 (100.0)
	Yes	3 (100.0)	0 (0.0)	3 (100.0)
Total		27 (81.8)	6 (18.2)	33 (100.0)

Table 2. Frequency of the various forms of unstable chromosomal aberrations (fUChA) at the previous/initial and periodical medical examination

	N	*fUChA on very first check-up, N (%)*	*fUChA on periodical check-up, N (%)*
Dicentrics	0	35 (89.7)	50 (87.7)
	1	4 (10.3)	7 (12.3)
Acentrics	0	32 (82.1)	38 (66.7)
	1	4 (10.3)	13 (22.8)
	2	3 (7.7)	5 (8.8)
Rings	0	38 (97.4)	53 (93.0)
	1	1 (2.6)	4 (7.0)
Chromatide lesions	0	36 (92.3)	45 (78.9)
	1	1 (2.6)	8 (14.0)
	2	2 (5.1)	4 (7.0)
Isochromatide lesions	0	35 (89.7)	44 (77.2)
	1	4 (14.0)	12 (21.1)
	3	0 (0.00)	1 (1.8)

Table 3. Frequency of acentric chromosomes at the previous/initial and periodical medical examination

		Acentrics on periodical check-up				*Total N (%)*
		0 N (%)	*1 N (%)*	*2 N (%)*	*3 N (%)*	
Acentrics at the initial check-up	0	14 (50.0)	10 (35.7)	3 (10.7)	1 (3.6)	28 (100.0)
	1	3 (100)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	2	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)	2 (100.0)
Total		18 (54.5)	10 (30.3)	4 (12.1)	1 (3.0)	33 (100.0)

p=0.025

Table 4. Frequency of isochromatide lesions at the previous/initial and periodical medical examination

		Isochromatide lesions on periodical check-up			*Total*
		0 N (%)	*1 N (%)*	*3 N (%)*	
Isochromatide lesions at the initial check-up	0	21 (72.4)	7 (24.1)	1 (3.4)	29 (100.0)
	1	2 (50.0)	2 (50.0)	0 (0.0)	4 (100.0)
Total		23 (69.7)	9 (27.3)	1 (3.0)	33 (100.0)

p=0.052

Regarding the isochromatid unspecific lesions the same outcome was observed– the number of people with the isochromatid lesions at the periodical check-up was higher (7 of them had 1 lesion and one had 3 lesions) (Wilcoxon Signed Rank test (p=0.052; Table 4).

By using the Student's t-test and comparing the haematological parameter values in periodical and initial examinations, higher values of the erythrocytes and monocytes at the periodical check-up were noticed (p<0.01; Table 5).

Applying the same test, no significant differences between the frequency of unstable chromosomal aberrations and the haematological parameters at the periodical check-up have been identified (p>0.05; Table 6).

The received 5-year cumulative dose did not have any influence on the increased frequency of the unstable chromosomal aberrations (Mann-Whitney U test, p>0.05; Table 7).

The connection between haematological parameters and the received 5-year cumulative dose at the periodical examination resulted in highly important negative correlation between reticulo-

Table 5. Hematological parameters at the previous/initial and periodical medical examination

Hematological parameters	*N*	*$\bar{x}$*	*SD*	*p value*
Red blood cells 0	65	4.064	0.404	<0.001
Red blood cells 1	65	4.279	0.437	
Reticulocytes 0	32	0.105	0.437	0.361
Reticulocytes 1	32	0.034	0.012	
White blood cells 0	62	5.865	1.301	
White blood cells 1	62	5.479	2.842	0.248
Monocytes 0	52	0.307	0.233	<0.001
Monocytes 1	52	0.474	0.232	
Neutrophils 0	47	4.020	3.944	0.899
Neutrophils 1	47	3.947	1.287	
Eosinophils 0	26	0.138	0.103	0.166
Eosinophils 1	26	0.293	0.531	
Lymphocytes 0	48	1.960	0.765	0.673
Lymphocytes 1	48	2.013	0.596	
Platelets 0	59	266.271	108.513	0.717
Platelets 1	59	260.536	65.233	

Table 6. Difference between frequency of the unstable chromosomal aberrations (fUChA1) and the hematological parameters in the periodical check-up

	fUChA 1	*N*	*$\bar{x}$*	*SD*	*p value*
White blood cells	No	49	5.81	2.67	0.454
	Yes	9	6.51	1.78	
Lymphocytes	No	42	2.03	0.69	0.775
	Yes	9	2.10	0.64	
Monocytes	No	42	0.48	0.24	0.981
	Yes	8	0.48	0.12	
Neutrophils	No	43	3.87	1.31	0.992
	Yes	9	3.86	1.26	
Reticulocytes	No	38	0.03	0.01	0.646
	Yes	7	0.04	0.01	

Table 7. Difference between frequency of the unstable chromosomal aberrations (fUChA) at the periodical check-up and received cumulative 5-year dose (cumulative personal dose equivalent/PDE)

	fUChA	*N*	*$\bar{x}$*	*SD*	*p value*
5 year PDE (mSv)	No	40	10.01	6.14	0.663
	Yes	7	8.96	3.12	

cytes and received cumulative dose in the 5-year period (Pearson`s coefficient linear correlation, p<0.01; Table 8).

As to the periodical check-up, the research about the influence of the length of exposure on the frequency of unstable chromosomal aberrations showed no statistical significance (Student's t-test, p>0.05; Table 9). On the other hand, the influence of the length of exposure on the haematological parameters, regarding the correlation between leucocytes and the length of exposure (p<0.05) has not been recorded, i.e. it was noticeable that the length of exposure had been directly connected with the increased leucocyte count (Table 10).

Discussion

According to the available literature, it is evident that an increase in the frequency of chromosomal aberrations is a response to a totally absorbed dose of ionizing radiation more than 100 mGy or 100 mSv [4,25].

The higher dose, as well as a long-term exposure to low doses, brings higher chances of getting leukaemia, while in the case of another form of tumors there is no clear statistical significance [26,27].

In addition, a long-term exposure to low doses of ionizing radiation increases the probabil-

Table 8. Correlation between hematological parameters in the periodical check-up and received cumulative dose for 5 years (personal dose equivalent/PDF)

		5-year PDE (mSv)	
	N	*R**	*p value*
Red blood cells	51	0.059	0.682
Reticulocytes	40	-0.484	0.002
White blood cells	51	-0.11	0.940
Monocytes	45	0.142	0.352
Neutrophils	45	0.001	0.996
Eosinophils	39	-0.055	0.740
Lymphocytes	44	-0.072	0.643

*Pearson's coefficient of linear correlation

Table 9. Difference between frequency of unstable chromosomal aberrations (fUChA) in the periodical check-up and duration of exposure

	fUChA1	*N*	$\overline{x}$	*SD*	*p value*
EWP	No	49	19.20	9.75	0.567
	Yes	9	17.22	7.69	

EWP: exposure work period

ity of unstable chromosomal aberrations, apart from the non-specific chromosomal lesions that were found at the unexposed examinees as well [4,9,28,29].

If during periodical examinations, an increase in the frequency of the unstable chromosomal aberrations and the increase in the number of micronuclei are recorded, the change of the employee workplace to a workplace without exposure to ionizing radiation has to be suggested for a period of 3 up to 6 months.

There are also cases where examinees have been 9 months away from the irradiation area, after which the follow-up check-ups showed a considerable decrease in the number of unstable chromosomal aberrations with the exception of nonspecific chromosomal lesions (chromatid and isochromatid), the decrease of which was not statistically relevant. It is believed that the survival of the lesions in some examinees indicates just a different repair mechanism, i.e. different length of recovery and individual sensitivity to radiation [21,29].

According to our study, comparing the periodical check-up to the previous/initial check-up, examinees had statistically higher frequency of acentric chromosomes and isochromatid, as well as nonspecific lesions. Every examinee with an increased frequency of the chromosomal aberrations at the periodical check-up had normal medical findings after working 6 months away from the previous workplace. In the period of several years of periodic check-ups, 6 examinees had at least two exclusions from the radiation zone. Presence of nonspecific chromosome lesions can indicate a higher probability of carcinogenesis [4,30].

A positive correlation was expected to be seen between the frequency of the unstable chromosomal aberrations of the received dose of x-rays and gamma-rays irradiation [9,16,17,28,31]. In our study, we found no correlation between frequency of the unstable chromosomal aberrations at the

Table 10. Correlation between hematological parameters in the periodical check-up and duration of exposure

		EWP	
	N	*R**	*p value*
Red blood cells	65	0.120	0.340
Reticulocytes	47	0.034	0.819
White blood cells	65	0.289	0.020
Monocytes	52	-0.029	0.837
Neutrophils	54	-0.212	0.124
Eosinophils	43	-0.083	0.598
Lymphocytes	53	-0.131	0.349

*Pearson's coefficient of linear correlation
EWP: exposure work period

periodical exam and the 5-year cumulative dose received.

Considering the examination of the employees exposed to irradiation, a decreasing tendency of the absolute lymphocyte count within reference values had been the only tendency response of the haematological parameters [26,27,32,33], only that nuclear medicine staff was at a higher risk of carcinogenesis [30].

In our research more attention was paid to the erythrocytes and monocytes at the periodical check-up as compared to the previous/initial ones. On the other hand, at the periodical check-up, after the received cumulative 5-year dose, there was a significant decrease in the reticulocytes count, probably due to the erythroblasts previous influence. We were also surprised to notice statistically significant increase of total leucocytes related to the working time under the exposure.

These unexpected results are opening questions on the role of the antioxidant system in the oxidative stress to which the organism had been exposed during the exposure to ionizing radiation [27,34-36]. The only explanation that could apply to this finding is that over the certain period of time, the immune system becomes enhanced due to the oxidative stress to which the organism had been exposed during the exposure to ionizing radiation [34-36].

It should also be taken into account that the majority of examined employees were women – the erythrocyte count (including precursors) varies according to the hormonal balance (menstrual cycle) during lifetime.

Regarding the occupational exposure to radionuclides for medical purposes, risk assessment of internal contamination is necessary due to the particularity of the workplace. Unfortunately, conventional gamma spectrometry measurement of urine is not always possible, especially since the new Law (i.e. Regulations of 2011) [3,23,37].

A current internal contamination was recorded by measuring and taking into account the half times of elimination and excretion. Considering nuclear medicine, in the case of exposure to low doses of ionizing radiation, a multiple gamma spectrometric measurement of 24-h urine is required. After the insight in the medical records of the examinees, only 19 of them underwent gamma spectrometric analysis of 24-h urine.

The results of this study suggest that the activity of radionuclides (131 I, 125 I, 99m Tc, 3 H) is within the limits of detection, i.e. in relation to the ALI (annual limit of intake) ranged from 0.1 to 10 Bq. Unfortunately the remaining 45 employees in the Nuclear Medicine Centre were not motivated to take part in this research. Limiting factors of this study were the lack of motivation among respondents, as well as irregularity of reporting to preventive-periodic medical examinations (apart from the existing legislation, the employer did not instruct the staff to do the check-ups).

It is also of great importance to recognize radiosensitive persons and to eliminate confounding factors in order to obtain adequate results of the biodosimetric tests [21,38]. Prior to the biodosimetric tests (analysis of the frequency of chromosomal aberrations and micronucleus test) each examinee filled in a questionnaire that provides information on smoking habits, alcohol consumption, drugs, potential exposure to ionizing radiation due to some diagnostic procedures in the last 3-6 months, exposure to chemical hazards (organic solvents, pesticides, heavy metals, etc.) as well as on possible recent viral infections and diseases. Apart from smoking, we took all information mentioned above into consideration when performing this study. For each survey it is very difficult to eliminate these confounding factors because there is a natural radioactivity to which we are all exposed, as well as the intake of heavy metals and pesticides, particularly through food and water [39].

Unfortunately, among 65 examined employees, 5 had thyroid disease (hypothyroidism, Hashimoto disease, thyroid nodules) while 2 of them had occupational disease (one professional cancer and one Hashimoto disease).

Correlation and differential diagnosis, as well as more sophisticated tests are necessary (Comet Assay, FISH, Premature centromere segregation) for detecting possible changes to the chromosomal material, a term that is important for long-term occupational exposure to low doses of ionizing radiation and easier diagnosis of occupational disease [14]. The main obstacle to more frequent implementation of such tests is the inability to financing research and procurement of adequate equipment.

Conclusions

According to the available data, it is certain that the long-term exposure to low doses of ionizing radiation may cause carcinogenesis.

Nuclear medicine professionals are exposed to increased health risks. Therefore, in order to prevent occupational diseases, it is compulsory to monitor their health condition at periodical examinations. Monitoring the frequency of chromosomal aberrations (with micronucleus test), haematological parameters and the received dose of ionizing radiation are necessary factors for the evaluation of the health condition, working ability assessment and diagnosis of occupational diseases.

Acknowledgement

In the memory and with gratitude to the late Professor Dr Snezana Milacic.

Authors' contributions

This study was designed by J. Djokovic-Davidovic and late S. Milacic. The manuscript was written by J. Djokovic-Davidovic with the suggestions of all authors. All the authors analysed and discussed the results.

Conflict of interests

The authors declare no confict of interests.

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