CHROMOSOMAL ABERRATIONS AND HEMATOLOGICAL ALTERATIONS AMONG RADIATION-EXPOSED HEALTH CARE WORKERS IN MANSOURA UNIVERSITY HOSPITALS, EGYPT.

By

Awaad AE[1], Kamel EA[1], Khashaba EO[1] and El- Dahtory FAM[2]

[1]*Department of Occupational Health and Industrial Medicine, Public Health and Community Medicine,*

[2]*Department of Biochemistry, Genetic Unit , Children Hospital, Faculty of Medicine, Mansoura University.*

Abstract

Introduction: The relationship between ionizing radiation (IR) exposure levels and the elevation of frequencies of different types of structural chromosomal aberrations (CA) is not yet completely clarified specifically at presumably chronic low-dose cumulative exposures. **Aim of work:** measurement of frequency of chromosomal aberrations (CA) and hematologic alterations in different radiation exposed occupational groups, verification of the presence of relevant health effects and measurement of accuracy of White Blood Cells (WBCs) count compared to chromosomal gene culture as biomarkers of exposure to IR. **Materials and methods:** A comparative cross-sectional study was carried out over a period of one calendar year in 2016 upon 97 Health Care Workers (HCWs) occupationally exposed to radiation in Diagnostic Radiology, Intervention Cardiology and Radiotherapy departments of Mansoura University Hospitals (MUHs) and a reference age- matched group of 50 HCWs unexposed to IR. They were subjected to interview-based semi-structured questionnaire including enquiries on socio-demographic data, full occupational history and clinical history and to blood sampling for both chromosomal culture and complete blood count analysis. **Results:** Significant reduction in the count of WBCs and lymphocytes among the exposed groups was found compared to reference group (p<0.001). This reduction was not revealed in MRI operators. Frequency of chromosomal aberrations increased significantly among radiologists, radiotherapists, interventional cardiologists (P<0.001, <0.001, 0.04; respectively). Significant positive correlation between frequency of aberrations and lifetime exposure score was found. The accuracy of WBCs count Area Under Curve (AUC=0.69) was estimated to be less than Chromosomal Culture (AUC=0.71). **Conclusion:** HCWs in Radiology Departments of MUHs may be considered to be exposed to higher-than-guidelines doses of IR. Chromosomal aberrations analysis can be used as a sensitive biomarker for IR exposure added to regular CBC done periodically in classified high-risk groups.

Key words: Occupational exposure, Low dose Ionizing radiation, MRI-Chromosomal culture and Interventional cardiology.

Introduction

Recent technological advances have greatly expanded the new modalities for use of ionizing radiation in diagnosis and treatment. For example, interventional radiology such as cardiac catheterization constitutes a source of relatively high exposure which is now heavily used (UNSCEAR, 2000). Another example is the extensive use of multi-slice computed tomography which has increased radiation doses received by HCWs and general public alike (Maher et al, 2004).

The relationship between low dose cumulative ionizing radiation exposure and the elevation of the frequencies of structural chromosomal aberrations is not yet completely clarified (Cordoso et al., 2004). Chromosomal abnormalities have been associated with genetic alterations that can trigger genomic instability and lead eventually to development of cancer (IAEA, 2001).

Numerous studies addressing the effects of partial or total body irradiation on peripheral blood cell count have focused on high-dose levels received accidentally or therapeutically rather than low dose radiation (Littlefield et al., 1991). Monitoring of personnel occupationally exposed to ionizing radiation usually depends on regular film dosimetry control and periodic examinations. Certain biomarkers provide more information which complements physical dosimetry and helps better evaluation of low-dose radiation exposure (Rozgaj et al., 1999). Moreover, little is known about the actual levels of exposure of Magnetic Resonance (MR) workers and health effects of their exposure, despite the prior existence of relevant national and international occupational exposure guidance (ICNIRP, 2010 and IEEE, 2005).

In Mansoura University Hospitals (MUHs), hundreds of HCWs are working with radiation. A radiation protection program has been instituted since decades. However, health complaints and enquiries arise from time to time. To the best of our knowledge, none of quality control measures has ever been used to test the existing health and safety programs.

Aim of work

Measurement of frequency of chromosomal aberrations (CA) and hematologic alterations in different radiations exposed occupational groups, verification of the presence of relevant health effects and measurement of accuracy of White Blood Cells (WBCs) count compared to chromosomal gene culture as biomarkers of exposure to IR.

Materials and methods

- **Study design:** A comparative cross sectional study.
- **Place and duration of the study:** The study was carried out over a period of one calendar year in the following departments of Mansoura University Hospitals (MUHs): Oncology and Nuclear Medicine department (radiotherapists), Radiology Unit of Emergency Hospital (radiology technician) and Cardiac Catheterization Unit in Cardiology department of Specialized Medical Hospital and MRI section in Radiology department.
- **Study sample:** The study was conducted upon 97 Health Care Workers (HCWs) occupationally exposed to radiation during their routine daily work and a reference age matched group of 50 HCWs whose work does not involve any exposure to radiation. All participants in the study including exposed and reference groups were 147 subjects.

The exposed group of the study was initially composed of 100 HCWs (technicians, nurses and physicians). Three workers were reluctant to undergo blood sampling letting the number of exposed group to be 97 HCWs. Inclusion criteria included workers regular on job for at least 4 years, dealing directly with the machines and free from acute or chronic infection at the time of the study. Their mean age was 38±6.4 years old and with mean duration of exposure 15.5±6.6 years.

The exposed group was classified into four subgroups based on the place of work:

First group (No=27): Technicians in Radiology Unit of Emergency Hospital.

Second group (No=25): Physicians and nurses in cardiac catheterization unit in Cardiology Department of Specialized Medical Hospital.

Third group (No =33): Radiotherapists in Radiotherapy unit of Oncology and Nuclear Medicine Department.

Fourth group (No =15): MRI operators in MRI unit of Diagnostic Radiology Department.

The Reference group of the study composed of 50 subjects, age-matched administrative workers in MUHs whose work doesn't involve any past or current exposure to radiation inside or outside job. Their mean age was 37.1±5.7 years old and work duration 13.5± 5.4 years.

- **Study methods:** All study participants were subjected to:

[redacted]

The questionnaire was filled by the [redacted]

B. Clinical examination: focusing on organ systems known to be affected by different types of radiation exposure including ocular, dermatological, thyroid, and breast examination.

C. Laboratory investigations: Peripheral blood sample was obtained for every subject in the study for both chromosomal culture and complete blood count (CBC). A 3 ml venous blood sample was collected and transferred immediately to the laboratories in Mansoura University

Children's Hospital. The blood sample was divided into 1 ml venous blood on EDTA for CBC and 2 ml venous blood on heparin for chromosomal culture.

C.1 Complete Blood Count: Hemoglobin in gm per dL, red blood cells count in millions per microliter (μL), total leucocytic count in thousands per μL, differential leucocytic count in % of total count, and platelet count in thousands per μL were performed.

C.2 Chromosomal culture: it was done according to the method described by Rooney and Czepulkowski (1997). Two milliliter of sodium-heparinized whole blood was collected from each individual. A blood sample of 0.5 cm 3 from each individual was added to 5 cm 3 of a complete media Roswell Park Memorial Institute (RPMI) 1640, fetal calf serum (10%), phytohaemoagglutinin (PHA) (10 μg/ml), L-glutamate (2 mM), penicillin (200 unit/ml), and gentamicin (50 μg/ml). After 72 h of incubation at 37°C, colcemid was added (0.2 μg/ml). After 90 min, the cells were harvested by centrifugation (150 × g for 10 min). Then, 5 cm 3 of cold fresh fixative solution was added to cell pellets. The metaphases were analyzed for chromosomal breakage by cytovision system. The mean spontaneous chromosomal breakage per cell for each culture was calculated.

Workplace description:

1. The Radiology Unit of Emergency Hospital (EH): Equipments: CT, plain X-ray and fluoroscopy unit for conventional and fluoroscopic examination. Work Flow: The radiology technicians in EH were working 12 hours per day for 3 days per week in 2 rotating shifts: Safety measures: Irregular use of PPE (81.5%) was reported despite the availability of lead aprons (88.9%) and absence of personal dosimetry control from badge films was observed.
2. Cardiac Catheterization Unit: Equipments: two fluoroscopy units for interventional cardiovascular procedures. Work Flow: Cardiologists work 6 hours per day once per week in rotating shift. The nurses were working 6 hours per day for 6 days per week. Safety measures: Regular wearing of lead

aprons (100%) and occasional wearing of thyroid shield (52%) were observed. But, neither protective eye goggles nor badge films were available.

3. The Radiotherapy Unit: Equipments: Teletherapy machines: simulator, Cobalt 60, linear accelerator SL-75, superficial radiotherapy unit RT-100 and linear accelerator SL-15. Simulator is out of function since 2012. Cobalt 60 machine, superficial radiotherapy unit RT-100 and linear accelerator SL-15 are out of function since 2008.Work flow: They were working 6 hours per day for 6 days per week in two rotating shifts. Safety measures: The lead apron were available to all of them (100%), however, it was not used , badge film was used by 45.5% of them with no physical measurement for personal doses received.

4. MRI Unit: Equipments: 1.5 Tesla MRI scanner Work flow: 12 hours per day for 2 days per week in one rotating shift from 8 am to 8 pm. Pattern of Exposure: They are mainly exposed to large static magnetic field (SMF) produced by the magnet of the MRI scanner and, additionally, experience low-frequency time-varying magnetic fields (TvMF) from movement through the static magnetic stray field around the scanner. They could also be exposed to RF radiations present only inside the scanner when the clinical needs force them to move close to the scanner during the examination (Karpowics et al., 2007and Franco et al.,2008).

Consent

An informed verbal consent was obtained from study participants before the start of study with assurance of confidentiality and anonymity of data.

Ethical consideration

Study Protocol was approved from Ethical Research Committee of Faculty of Medicine, Mansoura University.

Data management

Data were analyzed using the SPSS version 16 (SPSS, Chicago, IL, USA). Qualitative variables were described as numbers and percentages. Chi square (Fisher's exact test) was used for comparison between groups when 50% of cell value was less than 5.

Quantitative variables were described as mean (±SD), median, minimum and maximum. Mann-Whitney test was used to compare average chromosomal breakage between 2 different groups. Pearson's correlation coefficient was used to illustrate the relationship between two variables. Roc Curve was used to measure Area under curve (AUC) for WBCs and chromosomal analysis in relation to exposure status. P-value ≤0.05 was considered to be statistically significant.

Results

Socio-demographic characteristics of the study groups: There was no significant difference between exposed subgroups and reference group as regards age and smoking status (P>0.05).However, there was statistically significant differences between exposed subgroups and reference group as regards sex and education (P<0.05) which was difficult to control in four subgroups (Results are not tabulated).

Hematological findings of the studied groups: WBCs count was significantly lower among radiology technicians, HCWS in interventional cardiology and radiotherapy technicians compared to reference group (P<0.05). RBCs count was significantly lower among radiology technicians, HCWS in interventional cardiology and MRI operators compared to reference group (P<0.05). Moreover, platelet count was significantly lower among radiology technicians and radiotherapy technicians compared to reference group (P<0.05).Hemoglobin was significantly lower among HCWS in interventional cardiology and radiotherapy technicians compared to reference group (P<0.05). Lymphocytic count was significantly lower among diagnostic radiology technicians, HCWS in interventional cardiology and radiotherapy technicians compared to reference group (P<0.05). Finally, Neutrophils were significantly lower among diagnostic radiology technicians and radiotherapy technicians compared to reference group (P<0.05). In general, leucopenia (<4000/µL) was found among 5 subjects out of 33 radiotherapists (Results are not tabulated).

Table (1): Frequency of chromosomal aberrations per cell in the studied groups

Studied groups	Number of Subjects (No=147)	Frequency of Chromosomal Aberrations (CA)/cell Median (min.-max.)	p-value
Radiology technicians in Emergency Hospital	27	0.03 (0 - 0.09)	≤ 0.001**
HCWS in Cardiac Catheterization Unit	22	0.0 (0 - 0.08)	<0.05*
Technicians in Radiotherapy Unit	33	0.01 (0 - 0.09)	≤ 0.001**
MRI operators	15	0.0 (0 - 0.02)	>0.05
Reference group	50	0 (0.0)	

**: Highly significant *: Significant

Chromosomal culture findings of the study groups showed that the groups exposed to IR had more frequent chromosomal aberrations compared to the reference group with statistically significant differences ($P<0.05$). But, MRI operators had nearly comparable levels of aberrations to that in reference group as shown in Table 1.

Table (2): Frequency of different types of chromosomal aberrations per group.

Studied groups	No of meta-phases scored	Types of Chromosomal Aberrations							#CA per 100 cells
		Dicentric	Break	Gap	Fragment	Ring	Triploidy	Total	
Radiology technicians (No=27)	2700	21	66	16	2	1	1	107	3.96
Cardiac catheterization unit(No=22)	2200	7	10	5	1	2	0	25	1.14
Radiotherapy unit (No=33)	3300	20	36	11	2	0	1	70	2.12
MRI operators (No=15)	1500	0	5	1	1	0	0	7	0.47
Reference group (No=50)	5000	0	3	2	2	0	0	7	0.14

#CA/100 cells =total no of chromosomal aberrations per group / total no of metaphases scored per group× 100.

Table (2) shows that the most frequent type of chromosomal aberrations in radiology technicians, radiotherapists, catheterization and MRI groups to be breakage (66, 10, 36 and 5 breaks respectively) with higher total number of aberrations per 100 cells recorded among radiologists. Frequency of dicentric chromosomes for each group was found apparently to be higher among Radiology technicians (21), followed by Radiotherapy technicians (20), then HCWS in Cardiac catheterization unit (7). Dicentric chromosomes were not detected in the reference group or in the MRI operators group.

Table (3): ROC curve statistics for WBCS count and frequency of CA per cell as screening tests for exposure status to ionizing radiation.

Markers	AUC	SE	95% CI	Cut-off	Sensitivity	Specificity
WBCs(10^3/ul)	0.68	0.04	0.59-0.76	4.00	0.06	1.00
CA	0.71	0.04	0.63-0.79	0.035	0.20	1.00

WBCs: White blood cells
CA: Chromosomal aberration

AUC: Area Under Curve
SE: Standard error.

ROC curve analysis revealed that CA is better (AUC=0.71) than WBCs count (AUC 0.68) in determination of the exposure status.

Table (4): Correlation between frequencies of chromosomal aberrations, age, calculated life time exposure score, Lymphocyte count and WBCs count.

Parameters	Radiology technicians No=27	Intervention cardiologists No=22	Radio-therapists No=33	Ionizing Radiation group Total No=82	MRI operators No=15
	Frequency of chromosomal aberrations(CA)				
	r (p)	r (p)	r (p)	r (p)	r (p)
Age	-0.002 (0.9)	-0.11 (0.6)	0.13 (0.7)	0.1 (0.2)	0.1 (0.7)
Calculated Life time Exposure Score#	-0.04 (0.8)	0.2 (0.3)	0.1 (0.4)	0.26 (<0.05*)	-0.12 (0.6)
Lymphocyte count (10^3/uL)	0.11 (0.57)	- 0.5 (<0.05)*	- 0.3 (0.07)	- 0.24 (<0.05*)	-0.06 (0.8)
WBCs count (10^3/uL)	-0.26 (0.18)	-0.06 (0.7)	0.1 (0.5)	0.04 (0.7)	0.2 (0.3)

#calculated life time exposure= total work hours x 47weeks work x duration of employment in years.

*: Significant

There was significant positive correlation between frequency of CA and Lifetime exposure score in total IR group. There was significant negative correlation between lymphocyte count and CA in total IR group and intervention cardiology group.

Table (5): Medical complaints reported by the studied groups.

Medical complaints	Radiology technicians (No=27) No (%)	HCWS in Intervention Cardiology (No=25) No (%)	Radiotherapy technicians (No=33) No (%)	MRI operators (No=15) No (%)	Reference Group (No=50) No (%)	p-value Fisher's Exact Test
Ocular complaint	23(85.2%)	23(92%)	27(81.8%)	15 (100%)	14(28%)	P1<0.001* P2<0.001* P3<0.001* P4<0.001*
Eye strain	22(81.5%)	23(92%)	23 (69.7%)	15 (100%)	9(18%)	P1<0.001* P2<0.001* P3<0.001* P4<0.001*
Decreased visual acuity	14(51.9%)	19(76%)	25(75.8%)	15(100%)	14 (7%)	P1<0.05* P2<0.001* P3<0.001* P4<0.001*
Blurring of vision	11(40.7%)	14(56%)	19(57.6%)	15(100%)	5(10%)	P1<0.001* P2<0.001* P3<0.001* P4<0.001*
Eye irritation	7(25.9%)	4(16%)	14(42.4%)	9(60%)	1 (2%)	P1<0.001* P2<0.005* P3<0.05 * P4<0.001*
Symptoms suggesting cataract	7 (25.9%)	4(16%)	7 (21.2%)	3 (20%)	1(2%)	P1<0.001* P2<0.05* P3<0.05* P4<0.05*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	P1>0.05 [redacted] P4<0.05*
Hair loss on scalp or other parts	16(59.3%)	10 (40%)	15(45.5%)	0(0%)	10(20%)	P1<0.005* P2>0.05 P3<0.01 * P4>0.05

P1: statistical significance between radiology technician and reference group, P2: statistical significance between interventional cardiology and reference group, P3: statistical significance between radiotherapists and reference group, P4: statistical significance between MRI operators and reference group.

*: Significant

Table 5 showed that all ocular symptoms (eye strain, eye irritation, blurring of vision, decreased visual acuity and symptoms suggesting cataract) were significantly higher among the exposed group compared to the reference group ($p<0.05$). Dermatological lesions were significantly higher among radiotherapists compared to the reference group ($p<0.05$). Hair loss on scalp was significantly higher among diagnostic radiology technicians and radiotherapists compared to reference group ($p<0.05$).

There was statistically significant difference between exposed group and reference group as regards headache and dizziness ($p<0.05$). Parathesia was significantly higher among radiology technicians, radiotherapists and MRI operators compared to reference group ($p<0.05$). Metallic taste was significantly higher only among group of MRI operators compared to reference group ($p<0.001$). Memory problems were significantly higher only among group of MRI operators compared to reference group ($p <0.001$) (Results are not tabulated).

Discussion

The current study was done at Mansoura University Hospitals (MUH) to verify whether HCWs occupationally exposed to presumably controlled radiation sources during their routine work were really protected or not and to examine whether chromosomal aberrations could be used as biomarkers for possible radiation injury among these workers exposed to chronic low-dose of ionizing radiation in diverse health care settings.

Hematological results of current study (results are not tabulated)replicate what was found by Rozgaj et al. (1999) in a retrospective study conducted in a hospital in Croatia on 483 subjects divided in four groups doing X-ray examinations and 160 control subjects.

They demonstrated that long-term low doses exposure to of IR may affect the cells and tissues and resulting in different adverse health effects. The exposed groups manifested significantly lower values of the leukocyte count than did the controls. The incidence of leucopenia among the exposed groups was noted sporadically. The lymphocyte count in one pulmonologist was slightly below the limit, whereas no case of thrombocytopenia was found in any of the groups.

On the other hand, others as Khorrami and Riahi-Zanjan (2015) in their study on healthy workers of radiology department of a hospital in Mashhad revealed that there was no significant difference between exposed and referent groups as regards all hematological parameters except Platelet distribution width (PDW) and Platelet large ratio (P-LCR). The mean percentages of PDW and P-LCR of case subjects were found statistically to be higher than values of comparison group which may be related to adverse effects of radiation on platelet progenitor cells.

Our hematological results are most probably precipitated by occupational exposure to ionizing radiation which according to Takeuchi, et al., (1992) and Minoru and Hiroshi, (1997) has a destructive action on cells of the immune system depressing their activity such as antibody-producing ability, delayed type hypersensitivity reaction and mitogenic activity.

In the current study, hematological findings may point to the fact that workers in MUHs might be actually exposed to doses in the range of 100-500 mSv or even higher (Ionizing radiation regulation, 1999). Diminished RBCs and hemoglobin levels among the exposed group might point to the fact that routine occupational exposure to presumably chronic low doses was sufficient to affect RBCs hematopoiesis or that observed exposure had been in fact to higher doses than was originally expected .

Our results on frequency and type of chromosomal aberrations observed (Table 1) are similar to the findings of Maffei et al. (2002) who reported frequencies of aberrant cells and chromosome breaks to be significantly higher among hospital workers occupationally exposed to low levels of IR than in controls. Seven dicentric aberrations were detected in the exposed group and only three among controls, but the mean frequencies were not significantly different.

Also, A study in Zagreb, Croatia on 765 medical workers conducted on eight exposed groups (80 anaesthesiologists, 45 anaesthetic technicians, 250 radiology technicians, 100 operating room nurses, 100 surgeons, 50 nurses, 100 radiologists, and 40 urologists/ gynaecologists) and control group of 200 healthy volunteers reported that all types of aberrations were higher among the exposed groups than in controls except ring chromosomes. Ring chromosomes were not found in nurses, operating room nurses, or anaesthetic technicians. The most frequent type of aberrations found in exposed subjects was acentric fragment followed by dicentric chromosome, tri and tetra-radial exchanges and ring chromosome. The frequency of dicentric chromosome which is considered the most important aberration type indicating exposure to ionizing radiation, was higher among urologists/ gynaecologists (Kasuba et al., 2008). However, other researchers as Saberi et al. (2012) found higher frequency of CA among exposed angiography workers than those found in CT scan and radiotherapy workers.

Considering non significant correlation between frequency of CA and age (Table 4), results of current research agree with several authors (Jha and Sharma 1991; Chung et al. 1996; Miyaji and Mara 2002; Garaj-Vrhovac et al. 2006; Movafagh etal. 2007; Kausba et al. 2008). However, Ballardin et al. (2007) also found a slight increase in total chromosome aberration frequency with age.

Our work revealed that accuracy of chromosomal culture (AUC-0.71) as screening test was better than leucocytic count (AUC=0.68) in prediction of exposure status to IR (Table 3). That is why according to certain acts such as the Croatian Public Health Act, all people working in a controlled area have to be examined for CA every five years (starting with a pre-employment check-up) and for blood count every year. Subjects with aberrant findings should abandon the controlled area for 6-12 months, and are re-examined before they continue to work in the controlled area (Rozgaj et al., 1999).

However, the cost of chromosomal culture may constitute an obstacle for its integration into Egyptian occupational health and safety programs. In Egypt, according to health and safety regulations, periodic screening is done by CBC every 6 months and if leucocytic count is found to be < 4000 cc, the worker is exempted from work with IR (Egyptian Law No 59/1960).

Medical complaints reported by study groups (Table 5) are most probably attributed to the cumulative occupational exposure to IR at dose levels and rates which may surpass current annual dose limits adopted worldwide (Ionizing Radiations Regulations, 1999). It is emphasized that statutory dose limits are set at levels well below those at which deterministic effects will occur and so no changes should be detectable by clinical examination, routine blood examination or special examinations.

Recommendations

The lymphocytic gene culture is recommended to be used in bio-monitoring to workers exposed to low-dose of radiation in addition to CBC every six months, taking into consideration the relation between cancer and high frequencies of chromosomal abnormalities. Pre-employment examination is necessary for everyone who will work in an ionizing radiation zone, as well as effective implementation of personal protective measures. Regular medical examination every year is required to all exposed Ionizing and non-ionizing radiation workers. The workers with positive CA should be subjected to intensive occupational health and safety review and accurate measurement for radiation doses at the workplace.

Conflict of interest

There is no conflict of interest; and there weren't any funding agencies for this study.

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