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Retrospective cytogenetic biodosimetry using fluorescence in situ hybridisation (FISH) technique in persons exposed to radiation due to the Chornobyl accident

Ретроспективна цитогенетична біодозиметрія із використанням методу флуоресцентної in situ гібридизації (FISH) в осіб, які зазнали опромінення внаслідок катастрофи на Чорнобильській АЕС

Цель работы: Проведение цитогенетической биодозиметрии отдаленного и хронического облучения в низких дозах с использованием метода флуоресцентной in situ гибридизации (FISH) у лиц, подвергшихся радиационному воздействию вследствие катастрофы на Чернобыльской АЭС.

Материалы и методы: Забор образцов крови проведен через 9,5–14,8 лет после катастрофы на ЧАЭС у 16 ликвидаторов, 18 жителей, эвакуированных из 30-километровой зоны, 21 жителеля радиоактивно загрязненных регионов Белоруссии и 12 контрольных здоровых доноров соответствующего возраста. Цитогенетический анализ клеток 48-часовой культуры лифоцитов осуществляли с применением техники FISH (комбинации хромосом 1, 2 и 4 или 6, 9, 15 и 21; пан-центромерные зонды). Нестабильные и стабильные аберрации хромосомного типа регистрировали с использованием комбинированной классической/PAINT-номенклатуры. Для биологической оценки доз облучения в экспонированных группах рассчитывали надспонтанный уровень стабильных хромосомных обменов в клетках с полным наличием всего хромосомного материала, который соотносили с линейным членом калибровочной кривой «доза–эффект», построенной in vitro.

Результаты: Средняя частота дицентриков и колец, парных фрагментов и делетированных хромосом не имела статистических различий с контролем во всех группах лиц чернобыльского контингента. Уровень полных транслокаций был достоверно повышен у ликвидаторов и эвакуированных жителей, а суммарная частота неполных транслокаций — во всех трех экспонированных группах. Оценки дозы облучения по частоте стабильных хромосомных обменов составляли 300 мГр у эвакуантов и 390 мГр у ликвидаторов, что соответствовало результатам биодозиметрии с использованием классического анализа в ранние сроки после облучения в этих группах (соответственно, 360 и 460 мГр). У молодых жителей радиоактивно загрязненных территорий исследование методом FISH позволило детектировать среднюю дозу 150 мГр хронического облучения.

Выводы: Результаты исследования показали достаточную пригодность FISH-анализа для когортной биодозиметрии отдаленного и хронического облучения в низких дозах.

Ключевые слова: биологическая дозиметрия, лимфоциты, флуоресцентная in situ гибридизация, транслокации, катастрофа на ЧАЭС, отдаленное и хроническое облучение в низких дозах.

Objective: To carry out cytogenetic biodosimetry of past and chronic radiation exposure to low doses using fluorescence in situ hybridization (FISH) technique in persons exposed due to the Chornobyl accident.

Material and Methods: Blood samples were collected 9.5-14.8 years after Chornobyl accident in 16 liquidators, 18 Ukrainian evacuees from 30 km exclusive zone, 21 Belorussian inhabitants of radioactively contaminated areas and 12 control donors age matched to exposed groups. Cytogenetic analysis was performed in 48 h lymphocyte cultures using FISH technique highlighting chromosome combinations 1, 2 and 4 and 6, 9, 15 and 21 and centromeres of all chromosomes. Unstable and stable chromosome type aberrations were recorded using a conventional-PAINT nomenclature. For biological dose assessment the overspontaneous yields of stable chromosome exchanges in cells with full presense of chromosomal material were calculated in exposed groups and referred to a linear term of calibration dose-response curve constructed in vitro.

Results: The average levels of dicentrics plus centric rings, acentric fragments and deleted chromosomes in all three Chornobyl groups didn not show a statistical difference with control values. The levels of complete translocations were significantly increased in liquidators and evacuees, and the total incomplete translocation yield was elevated above the control in all three exposed groups. Biological dosimetry based on stable chromosome exchange yield provided the dose estimations of 300 mGy in evacuees and 390 mGy in liquidators, that were in a good agreement with dose assessments obtained in these groups soon after irradiation with conventional analysis (360 and 460 mGy, respectively). The FISH survey of young adult inhabitants of contaminated areas allowed detecting the chronic exposure at average dose of 150 mGy.

Conclusion: The results of investigation showed a sufficient applicability of FISH analysis to cohortal biodosimetry of past and chronic radiation exposure to low doses.

Key words: biological dosimetry, lymphocytes, fluorescence in situ hybridization, translocations, Chornobyl accident, past and chronic radiation exposure to low doses.

The catastrophe at the Chornobyl Nuclear Power Plant happened in April 1986 was an example of a large-scale radiation accident leading to overexposure of significant number of individuals among general public. Due to this accident the population from 30-km exclusive zone and some regions highly contaminated with radionuclides was evacuated, several thousands of liquidators were

irradiated during the clean-up operations and more people still had to live in the areas with increased levels of radioactivity deposition in the ground [1]. The cohorts of liquidators, evacuees and inhabitants of radioactively contaminated regions were exposed mainly to low-dose protracted or chronic irradiation that did not cause deterministic health effects in the majority of cases. But whatever low, the levels of overexposure in post-Chornobyl critical groups need to be evaluated thorougly for late somatic and genetic risk assessment, that became a real challenge for epidemiology and biological dosimetry.

The chromosomal analysis of blood lymphocytes appeared to be the technique of choice for both genetic impact monitoring and biodosimetry in Chornobyl cohorts [2-7]. However, it became obvious,that any attempts of applying the conventional cytogenetics based on unstable aberrations analysis several years after the accident would not give sufficient results for biological dosimetry due to elimination of cells carrying dicentrics from the circulating lymphocyte pool [4-6]. Therefore the alternative approach based on stable chromosome rearrangements quantification should be used for estimating the yield of cytogenetic damage in lymphocytes of exposed persons.

Among currently available techniques for stable aberration visualising the fluorescence *in situ* hybridisation (FISH) seems to be the most appropriate one, allowing the rapid identification of two main stable cytogenetic end-points — translocations and insertions [8]. The experience of FISH applications for *in vivo* and *in vitro* studies has showed the advantages of this method, and also some limitations have been recognised and partially solved. One of the problems was related to finding out a proper way of calibrating the FISH biodosimetry system,and several approaches to dose-response curve constructing were proposed [9-12]. Another confounding factor was a quite high and variable spontaneous level of stable aberrations in unexposed population with a clear tendency for increasing of translocation yield with donor's age that caused a necessity of age-matched control or empirical age-effect regressions to be present in any *in vivo* survey [13, 14]. As a result of *in vitro* and *in vivo* observations it was concluded that FISH assay should be preferentially used for investigations of past and long term chronic exposures to low doses [15]. However, the data obtained in humans exposed protractedly or chronically to low dose radiation appeared to be controversial: in some cases the FISH-based retrospective dosimetry was successful [15-17],but other attempts failed to distinguish exposed and unexposed populations by comparing their levels of FISH-detectable translocations [18, 19]. Thus, more data coming from *in vivo* surveys still need to be accumulated for estimating the practical value of FISH analysis in human peripheral lymphocytes as a retrospective biological dosimeter. For strengthening the conclusions, the FISH assay has to be concentrated primarily on those groups, which have been already investigated with routine cytogenetic technique soon after irradiation, that may allow to perform a direct comparison of doses measured by dicentric analysis with those detected by FISH.

This paper presents biological dose assessments based on measuring of stable chromosome aberration levels in liquidators, evacuees from Chornobyl exclusive zone and inhabitants of radioactively contaminated areas sampled late time after the Chornobyl accident, that was a part of long-term cytogenetic monitoring carried out in post-Chornobyl cohorts at Institute for Medical Radiology, Kharkiv, Ukraine.

Materials and methods

Study groups

Liquidators group included 13 males and 3 females, age ranged from 35 to 48 years (mean 41 years). They were residents of Kharkiv region, who carried out different kinds of clean-up operations or civil service at the Chornobyl zone in 1986-87 and were sampled within 9.5-14.8 years after exposure.

Evacuees group consisted of 11 females and 7 males, former residents of town Pripiat and nearby villages. They were evacuated soon after the accident to Kharkiv region and sampled within 12.8-14.8 years after departure from the Chornobyl exclusive zone; age at the time of sampling ranged from 16 to 55 years (mean 40 years).

The group of inhabitants of radioactively contaminated regions of Belarus included 15 females and 6 males. They were children at the time of the Chornobyl accident and continued to live in areas with increased levels of radionuclide deposition in the ground; age varied from 15 to 26 years (mean 21 years) at the time of their sampling which was performed 12.8-14.8 years after the Chornobyl accident.

Control group consisted of 7 females and 5 males, unexposed inhabitants of Kharkiv region aged from 19 to 58 years (mean 39 years), who were selected in trying to cover the age interval for all three exposed groups.

Blood sampling of liquidators and evacuees was carried out at the Institute of Medical Radiology (Kharkiv, Ukraine). Blood samples from the Belorussian group were collected at the Institute of Genetics and Cytology (Minsk, Belarus) and passed to the National Radiological Protection Board of the United Kingdom (NRPB) for cell culturing, then coded preparations were transferred to the IMR for further FISH analysis.

Cell culuring, FISH painting and aberration scoring

The details of techniques and aberration scoring criteria were published earlier [12, 20]. Briefly, the standard method of peripheral blood lymphocyte culturing was applied with PHA-stimulated lymphocyte cultures setting up for 48 hrs, metaphases harvesting after 4 hrs colchicin treatment and fixing in methanol/acetic acid mixture [8]. From each sample replicated slides were prepared, coded and processed by FISH technique according to the protocol of NRPB Cytogenetic Lab [9]. Slides were FITC painted, highlighting chromosome combinations 1, 2 and 4 or 6, 9, 15 and 21 (Cambio), other chromosomes were counterstained with DAPI (diamidino-2-phenylindole), pancentromere probes (Oncor) that fluoresced red were also applied.

Slides were examined under fluorescence microscopes (Nikon, Zeiss) equipped with filter sets for FITC, DAPI and all three fluorochromes visualizing. Aberrations were counted in cells containing 46 centromeres and diploid amount of painted material from FITC-highlighted chromosomes. Translocations were recorded using the hybrid modification of conventional/PAINT descriptive nomenclature as complete t_{comp} or incomplete t_{inc}Ab and t_{inc}Ba. The latter were subdivided into three subgroups: involving an unshortened painted chromosome – t_{inc}Ba*, accompanied by a fragment from the painted chromosome – t_{inc}Ba+ac, involving a markedly shortened chromosome with no missing painted fragment present somewhere in the cell – t_{inc}BaMP ("missing part"). Insertions of Aba and Bab-types were pooled into one category. Each exchange, either complete or incomplete, was accounted as an entity. Deleted painted chromosomes with a segment absent, dicentrics and centric rings accompanied by fragment and excess acentrics in painted chromosomes were also recorded for data completness.

Statistical analysis

Numbers of actual cells scored were converted into genome equivalents using a monocolour version of Lucas' formula for the sum of DNA content in highlighted chromosomes [21, 22]. Individual scoring data were pooled within each group; mean yields of aberrations were expressed per 100 genome equivalents. Standard errors for the means were calculated from the dispersion of individual aberration yields within a group. For intergroup data comparison Student's *t*-test was applied.

Results and discussion

Actual numbers of unstable and stable chromosome type aberrations and their yields per 100 genome equivalents in groups of liquidators, evacuees and inhabitants of contaminated regions are shown in Table 1. Cytogenetic parameters in liquidators and evacuees were compared directly to those of in total control group due to similarity of mean age values. The spontaneous levels of translocations, insertions, acentrics and deleted chromosomes for inhabitants were calculated using age-effect regressions constructed in control group previously [20]. Metaphases with complex rearrange ments were rare and all aberrations from the complexes were included into appropriate columns of Table 1. Individual aberration yields appeared to be randomly distributed in consistence with Poisson statistics within each group.

The average levels of dicentrics plus centric rings and acentric fragments in liquidators and evacuees were slightly increased above control, but no statistical difference was observed ($p>0.05$). The level of unstable aberrations in inhabitants group was even more close to spontaneous parameters than that of evacuees and liquidators. That was in a very good agreement with a general picture of cytogenetic effects measured in these cohorts by conventional method late time after the acident [4-6]. The absence of unstable aberration frequency increase in exposed persons was considered as a result of elimination of lymphocytes with unstable aberrations from the circulating pool during years post-irradiation.

In contrast to unstable aberrations, the average yields of stable rearrange ments were markedly increased in exposed groups above control. However that was related mainly to exchanges, but not to deleted chromosomes. This type of chromosomal abnormalities was rarely reported to be measured in exposed persons, because they obviously resulted from the lost of chromosome acentrics or chromatid breaks during mitosis of the lymphocyte precursors, where fragments were initially induced. Both types of predecessor unstable aberrations have no exclusivity to radiation, so a low sensitivity of deleted chromosomes as an exposure marker after protracted or chronic irradiation to low doses could be concluded. Unlike deleted chromosomes, the stable chromosome exchange yields were increased above control, and the meaningful difference with spontaneous level occurred for t_{comp} and t_{inc}Ab in liquidators ($p<0.05$), t_{comp} in evacuees ($p<0.05$), t_{inc}Ab, t_{inc}Ba* plus t_{inc}Ba+ac and insertions in inhabitants ($p<0.05$-0.01). The total level of incomplete translocations was statistically elevated in all three exposed groups ($p<0.05$-0.001). Noteworthy, the sum of incomplete translocations was 1.9-2.6 times higher than the level of complete ones. The ratio of t_{inc}Ab to total t_{inc}Ba translocations had similar values in different groups: 1:0.6 in li-

quidators, 1:0.9 in evacuees and 1:0.7 in inhabitants.

The cytogenetic parameter applied for biological dosimetry was the yield of stable exchanges with actual or assumed full presence of chromosomal material in “stable” cells. That represented a combination of complete translocations, insertions, incomplete translocations $t_{inc}Ba^*$ and virtual proportion of $t_{inc}Ab$ involving unshortrened chromosome — $t_{inc}Ab^*$. The reasons of choosing this particular combination of parameters instead of total translocation level for practical purposes of retrospective biodosimetry were discussed previously [12].

Particularly, it was suggested that incomplete translocations with “missing part” had no exclusivity to ionizing radiation and may occur as a result of segregations of chemically-induced balanced chromatid exchanges in dividing lymphocyte precursors [23]. The presence of increased level of chromatid exchanges in liquidators, evacuees and inhabitants of contaminated areas was reported in several independent studies [2-4]. Thus for preciseness of radiation exposure detection the data analysis in Chornobyl groups has to be restricted to chromosome exchanges in cells with full presence of chromosomal material. Additionally, incomplete translocations accompanied by acentric fragments were also withdrawn due to instability of their wholeness during mitotic divisions of lymphocyte precursors. Elimination of acentrics would result in a lack of genetic material following by cell death or arising of incomplete translocations with “missing part” in daughter lymphocytes. It should be noted, that amongst three exposed groups a significant number of $t_{inc}Ba+ac$ was detected only in inhabitants of radioactively contaminated areas, that obviously reflected the radiation induction of this type exchanges directly in mature cells during lymphocyte lifetime. Therefore, the cytogenetic assessment of radiation doses accumulated years ago or during long term chronic exposure has to be based on the yield of chromosome exchanges formed without accompanying acentrics. Amongst incomplete translocations these were unshortened chromosomes with joined counterstained material, that probably represented reciprocal exchanges involving a small telomeric region beyond the limits of visual resolution by FISH. Assuming the identity of the mechanisms of tAb and tBa exchanges formation, the yield of $t_{inc}Ab^*$ was calculated withmultiplying the number of total $t_{inc}Ab$ by the respective fraction of $t_{inc}Ba^*$ within total $t_{inc}Ba$ in each studied group.

The calibration dose-response curve for the mentioned end-point was constructed *in vitro* within a low dose range (up to 1 Gy) and fitted to a linear-quadratic model [12]. Taking into account the protracted exposure conditions in all three Chornobyl groups the biological dose assessment was performed using only the initial linear slope of the curve, that was expressed by equation:

$$Y = c + 1.401 \cdot D, \qquad (1)$$

where Y is the aberration yield per 100 genome equivalents, c is the background incidence and D is dose in Gy. The spontaneous level for liquidators and evacuees was established in the total control group, and that for inhabitants was calculated using the empirical age dependence regression based on earlier published data:

$$Y_{Sp} = 0.11 + 2.68 \cdot 10^{-4} \cdot A^2, \qquad (2)$$

where Y_{Sp} is the full genome yield per 100 cells and A is age in years [12, 20]. The yields of stable exchanges and corresponding radiation dose estimations in Chornobyl groups are presented in Table 2. Dose errors were calculated applying Poisson standard errors for the excess of aberration level above control.

The results of retrospective FISH biodosimetry in liquidators and evacuees appeared to be in a good agreement withearly dose estimates based on conventional aberration scoring during first few months after departure from the Chornobyl zone. The errors of the dose estimates were higher in case of FISH biodosimetry, that was related to a larger dispersion of the spontaneous levels of stable chromosome exchanges. Another common tendency for the both cohorts was slightly lower dose values resulted from FISH analysis in compare with those obtained with dicentric method. Such effect may reflect some differencies in contents of groups surveyed early and late time after

Table 1

Aberration levels measured by FISH technique in Chornobyl groups comparing with controls

Group (n)	Genome equivalents scored	Aberration frequencies ±SE per 100genome equivalents (actual numbers are given in parenthesis)							
		Dicentrics +Rings	Acentric fragments	tcomp (Ab+Ba)	t_{inc} (Ab)	t_{inc} (Ba*), (Ba+ac)[a]	t_{inc} (BaMP)	Insertions	Deleted chromo-somes
Liquidators (16)	2223	0.22±0.09 (5)	1.03±0.21 (23)	0.72±0.12 (16)	0.85±0.15 (19)	0.09±0.04 (2)	0.41±0.10 (9)	0.13±0.07 (3)	1.62±0.17 (36)
Evacuees (18)	5282	0.17±0.05 (9)	0.98±0.13 (52)	0.57±0.07 (30)	0.63±0.10 (33)	0.15±0.07 (8)	0.44±0.10 (23)	0.13±0.06 (7)	2.08±0.27 (110)
Total controls (12)	4088	0.10±0.04 (4)	0.66±0.11 (27)	0.37±0.05 (15)	0.42±0.06 (17)	0.07±0.03 (3)	0.29±0.06 (12)	0.07±0.04 (3)	1.44±0.12 (59)
Inhabitants (21)	7916	0.10±0.03 (8)	0.71±0.12 (56)	0.29±0.05 (23)	0.44±0.07 (35)	0.10±0.03 (8)	0.21±0.05 (17)	0.09±0.03 (7)	1.20±0.14 (95)
Spontaneous levels for inhabitants (mean age 21 yrs)[b]		0.10±0.04	0.54±0.16	0.22±0.02	0.27±0.02	0.00	0.18±0.02	0.02±0.01	1.17±0.04

[a] – one t_{inc} (Ba+ac) was detected in the control group, one in evacuees group, six in inhabitants group and none in liquidators;
[b] – applying age-effect regressions for complete translocations, insertions and deleted chromosomes and real yields of acentrics and incomplete translocations observed in a subgroup of young control donors [6].

Table 2

Radiation dose estimates based on FISH analysis in Chornobyl groups comparing with biodosimetry data obtained with conventional analysis in early terms after exposure

Exposed groups	Late FISH assay			Early conventional assay	
	Exchanges in stable cells /100genome equivalents		Average radiation dose, mGy	Dicentrics+centric rings /100 cells	Average radiation dose, mGy
	Exposed	Control			
Evacuees	0.97 ± 0.14	0.55 ± 0.09	300 ± 130	1.25 ± 0.13[a]	360 ± 16[a]
Liquidators	1.10 ± 0.21	0.55 ± 0.09	390 ± 180	1.47 ± 0.10[b]	460 ± 30[b]
Inhabitants	0.44 ± 0.06	0.23 ± 0.11	150 ± 90	Not done	

[a] – data from [6]; [b] – data from [7].

exposure, but more likely it can be explained by non-absolute stability of translocation yield with time even after low dose irradiation.

The literature data concerning dose estimations obtained with FISH analysis in Chornobyl cohorts showed that biodosimetry performed by other authors were based on measuring the yield of either complete translocations alone or total translocations (including those with missing part of chromosomal material) [24-30]. Our present work seems to be one of the firsts where the splitting translocations into "full presense of chromosomal material" and "missing part" categories had been applied for biodosimetry *in vivo*. Therefore our data have to be better compared with total translocation levels observed in Chornobyl groups, than with dose estimations made by other laboratories.

In liquidators the reported mean yields of total translocations per 100 genome equivalents were 0.80-1.70 [24], about 1.20 [25], 0.98-1.43 [26], 1.24 [27], 1.77 [28] and 1.0-2.4 (complete translocations only) [29, 30]. After subtracting the spontaneous levels the remaining excess yields were 0.20-1.10 [24], 0.8-0.9 [25], 0.66-1.11 [26], 0.52 [27], 1.05 [28], and 0.5-1.9 [29, 30], that is comparable with overspontaneous yield 0.92 per 100 genome equivalents for total translocations in liquidators of our survey. In the majority of these publications the aberration levels were referred to calibration curves for acute exposure, and the resulted radiation dose estimations were 90 mGy [28], 250-270 mGy [25], 100-300 mGy (individually up to 1000 mGy) [26]. If translocation yield was converted into protracted irradiation dose, the biodosimetry estimates were 40-280 mGy

[24], 480 mGy [29], 246-549 mGy (in groups with recorded doses <1 Gy) [30].

In case of evacuees the excess of total translocation level appeared to be slightly higher in our survey (0.64 per 100 genome equivalents) than that of 0.41-0.55 for children and 0.28-0.36 for adults investigated by cytogeneticists from St. Petersburg [27, 31]. The mean overspontaneous yield of translocations was 0.32 per 100 genome equivalents and converted into dose about 42 mGy, but this result was obtained using an acute calibration curve with very high linear coefficient 6.41 per 100 cells per Gy [31].

In two reports the yields of translocations in populations from different regions contaminated with radionuclides were lower than in our study — 0.37 [32] and 0.32-0.54 per 100 genome equivalents [33]. But control levels in those publications were also low (0.26 and 0.11 per 100 genome equivalents, respectively), so the excess values were in agreement withour result (0.37 per 100 genome equivalents). Another study of Belarussian inhabitants of radioactively contaminated regions showed the translocation yields 1.10-1.80 per 100 genome equivalents, that were markedly higher than a reference control (0.6 per 100 genome equivalents) and corresponded to doses of protracted irradiation 180-400 mGy depending on the living place location [24].

In general, our results of measuring the translocation yields in three groups of persons exposed due to Chornobyl accident were in a good agreement withother data presented in literature. Some discrepancies in biological dose estimations could be related to the differencies in calibration systems applyied for retrospective FISH biodosimetry. Our approach regarded the specificity to ionising radiation and potential stability of aberrations employed for referring to dose response curve, also the spontaneous accumulation of stable rearrangements with persons' age and protracted irradiation conditions were taken into account. That allowed to obtain the retrospective dose estimations, which were rather close to early biodosimetry data in Chornobyl groups. Thus,the FISH method seems to be suitable for providing meaningful practical results for biological dosimetry of past and chronic radiation exposure to low doses.

Conclusions

1. The cytogenetic survey carried out late time after the Chornobyl NPP accident showed the significantly increased level of FISH measured stable chromosome exchanges in liquidators, Ukrainian evacuees from the Chornobyl zone and Belorussian inhabitants of radioactively contaminated areas in compare with controls.

2. Retrospective FISH biodosimetry in persons exposed to low dose radiation required a careful choosing the cytogenetic end-points with taking into account radiation specificity and potential stability of aberrations, that restricted the appropriate spectrum of chromosome rearrangements to complete translocations, insertions and incomplete translocations formed without accompanying acentrics in cells with full presense of chromosomal material.

3. Biological dosimetry based on stable chromosome exchange yields provided the dose estimations of 300 mGy in evacuees and 390 mGy in liquidators that were in a good agreement with dose assessments obtained with conventional analysis in these groups soon after the accident. The FISH survey of inhabitants of contaminated areas allowed detecting the chronic exposure at average dose of 150 mGy. The results of investigation confirmed the sufficient informativity of FISH analysis for cohortal retrospective dosimetry of past and chronic radiation exposure to low doses,despite some limitations and problems still need to be solved.

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