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Features of the Course of Various types of Stroke in Patients Exposed to Low-dose Radiation

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Abstract

BACKGROUND: There is limited number of studies about peculiarities of cardiovascular diseases in population of different region by the zone of radiation exposure risk.

AIM: The aim of the study was to study the effect of radiation factor on the pathogenesis of stroke.

MATERIALS AND METHODS: To study the in influence of radiation factor on pathogenesis of stroke, 358 stroke patients were distributed based on the place of their residence into corresponding zones of radiation risk: 53 patients lived in zone of extremely high radiation level (488–100 cSV, zone I): 75 - from the zone of maximal radiation exposure (35–100 cSV, zone II), 158 - from zone with high radiation exposure (35–7 cSV, zone III), and 72 patients were the residents of minimal radiation risk (1–7 cSV, zone IV).

RESULTS: The study of coagulation hemostasis had revealed the significant increase of fibrinogen level in patients from zone I: 4.7 ± 0.14% versus 3.2 ± 0.11%, in patients living in minimal radiation risk zone ($p < 0.01$). The patients from extremely high radiation risk had significant decrease in fibrinolysis time in comparison to patients from zone IV ($p < 0.05$). The primary APS was diagnosed in 24 (6.7%) patients in total group of stroke patients (11 males and 13 females), from which 21 patients with ischemic stroke and 3 with hemorrhagic stroke. Leiden Va defect was found significantly more often in patients lived in high radiation risk zone (9.4%), in 13.5% stroke patients from zone II, in 13.2% patients lived in zone I, in comparison to 6.9% patients lived in zone IV. The patients from zone I had significantly higher level of plasma homocysteine in comparison to patients from other zones, ($p < 0.01$). Furthermore, the significantly higher levels of plasma homocysteine were found in the group with maximal and high radiation exposure, in comparison to the group of patients from minimal risk zone ($p < 0.05$).

CONCLUSIONS: We can see the presence of indirect evidences of modifying influence of radiation factor on pathogenic mechanisms of stroke.

Introduction

For many years, from the moment of the atomic bombing of two Japanese cities Hiroshima and Nagasaki in 1945, the date of the start of exposure of large populations during testing the nuclear weapons, the date of Chernobyl catastrophe in 1986 and the numerous fact of radioactive outburst in different parts of the world [l], [2], [3], the researchers are continuously studying the problem of the radiation influence on the population.

There are limited number studies exist reporting that non-cancerous diseases, namely, cardiovascular diseases, could be remote outcomes of the radiation exposure.

The life span study finalized in 1997, was based on the analysis of long-term observation of 86,000 survivors of atomic bombing in 1945, showed that mortality from non-cancerous diseases was 14% higher (90% CI: 9–19%) at dose 1 sSv during 30 years of observation.

The analysis of the same cohort conducted by Shimizu *et al*., 1999 showed an increase in mortality from non-cancerous diseases only at high doses of radiation [4]. After longer observation of the same cohort, the analysis showed the statistically significant association of mortality rate with the dose of exposure, particularly in cardiovascular events heart and stroke [5], [6]. The study also has estimated the input of radiation factor in consideration with traditional risk factors of cardiovascular diseases, such as smoking. The study conducted by Wong *et al*., 1993 had also showed the same association of stroke mortality with the dose of radiation exposure [7], [8].

The Shimizu study shows that about 9600 people died because of stroke among the population of the cities of Hiroshima and Nagasaki in the period of 1950–2003, while the excess relative risk was 9% (95% CI 1–17%, $p = 0.02$). In this study, it was also determined that a dose of 0.5 g is associated with increased risk of stroke, including fatal [9], [10].

Recent studies have demonstrated a link between chronic radiation exposure and the development of endothelial dysfunction [11].

Thus, the increased production of reactive oxygen species under such conditions leads to an increase in the level of pro-inflammatory cytokines, a decrease in thrombomodulin and an increase in the level of plasminogen-1 [12].

As a result of progressive endothelial dysfunction, arterial hypertension develops atherosclerosis progresses. At the same time, it was found that the threshold level of radiation in such conditions is 0.4 g. Sasaki *et al*. in their study has showed the statistically significant effect of radiation on remote changes of systolic and diastolic pressures. This phenomenon researches associated with the degenerative effect of radioactive factor on cardiovascular system [13].

Early clinical studies have shown that heart is relatively resistant to radiation exposure. At high doses of radiation the fibrosis pericarditis and degenerative myocarditis usually occurs. The main pathological changes occurring in cardiovascular system at low doses of radiation are stenos and occlusion of large arteries and vasculopathy [14], [15]. The particular types of cytokines and growth factors, such as TGF-β1 and IL-1β, can stimulate induced by radiation proliferation of endothelium, fibroblasts, increased collagen storage, further fibrosis, and followed by apoptosis and progression atherosclerotic changes. The numbers of experimental studies have shown that the proliferation smooth muscle in large vessels could be characterized as the early stages of atherosclerosis in irradiated animals [16].

There is limited number of studies about peculiarities of cardiovascular diseases in of population of Semipalatinsk region by the zones of radiation risk exposure [17], [18], [19].

The fundamental difference here is the zone of the Semipalatinsk nuclear test site, whose population has been exposed to low doses of ionizing radiation for a long time. From 1949 to 1989, more than 450 nuclear tests were conducted at the Nuclear Power Plant in Kazakhstan. The zone of chronic radiation exposure thus formed led to a significant increase in cardiovascular diseases, primarily stroke [20].

Thus, the purpose of this work is to study the pathogenetic characteristics of various types of stroke in the zone of chronic radiation exposure.

Materials and Methods

To study the influence of radiation factor on pathogenesis of stroke, 358 stroke patients were distributed based on the place of their residence into corresponding zones of radiation risk: 53 patients lived in zone of extremely high radiation level (488–100 cSV, zone I); 75-from the zone of maximal radiation exposure (35–100 cSV, zone II); 158-from zone with high radiation exposure (35–7 cSV, zone III) and 72 patients were the residents of minimal radiation risk (1–7 cSV, zone IV), (Figure 1).

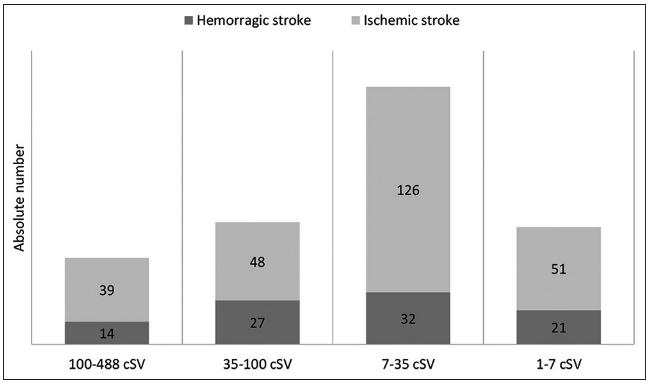

Figure 1: Distribution of stroke patients by radiation exposure zones

The estimation the influence of radiation risk on pathogenic mechanisms of stroke in the region, with the above mentioned approach, can only allow to approximate the indirect effects of the radiation as the environmental factor.

The age range of 358 stroke patients was from 28 to 82 years, (the average 60.5 ± 1.7), 264 (73.7%) ischemic, and 94 (26.2%) hemorrhagic stroke. From 264 patients with ischemic stroke 146 were male (the average age 59.1 ± 2.4 years) and 118 females (the average age 62.3 ± 1.5 years). From 94 patients with hemorrhagic stroke 49 (52.1%) were males (average age 54.3 ± 1.3 years) and 45 (47.8%) females (the average 59.4 ± 1.6 age).

Figure 1 shows the distribution of stroke patients by zones of radiation risk: in zone I 26.4% were with hemorrhagic stroke and 73.6% with ischemic stroke; in zone II 35.2% were with hemorrhagic stroke and 64.8% with ischemic stroke; in zone III 25.3% were with hemorrhagic stroke and 79.7% with ischemic stroke; and in zone IV 28.8% were with hemorrhagic stroke and 70.8% with ischemic stroke. There were no significant differences in distribution of stroke patients by zone of radioactive exposure.

Results

The results of the study of hemostasis parameters in stroke patients by zones of radiation exposure are presented in Table 1.

The investigation of aggregation activity of platelets in stroke patients from zone with (100–488 sSV)

Table 1: The comparative analysis of hemostasis parameters in stroke patients by in zones of radioactive exposure

Hemostasis parameters	Zones of radiation risk			
	100–448 ssv, (n = 53)	35–100 ssv, (n = 74)	7–35 ssv, (n = 158)	0.1–7 ssv (n = 72)
ATI,%	54.3–£5.7*	46.4 a4.7	42.1–£6.8	41.14–£2.6
SATI, %	56.2–£6.7*	36.4-£4.7	38.1–£4.1	36.5–£3.7
PDI, %	24.1–£2.4	26.1a2,3	23.1–F2.6	22.4–£2.2
Villebrand factor, %	101.4–£6.3	105.6+4.3	114.3–£6.2	112.8–£8.3
Fibrinogen , g/l	4.7–£0.14**	3.6z0.12*	3.3–s0.7	3.2–£0.11
RIA, s	12.9–£0.5*	13.7-£0.38	13.9–0.25	14.5–£0.18
VIA, s	14.8–£0.48	14.9-£0.66	14.9–£0.66	15.1–£0.17
APTT, c	34.2–£0.82	34.4+6,6	34.2a0.82	35.2–£0. 72
ATIII, %	73.1–s0.8	73.4-£0.95	73.2–£0.5	72.1–£0.9
Fibrinolysis, min	9.7–£0.17*	8.7z0.42	8.3–£0.53	7.8z0.44
SFMC, mkg/dl	9.3–£0.32*	8.8z0.91	8.2–£0.42	8.1–£0.23

*The comparisons done with patients with minimal risk group (0.1–7 sSV) significant, $p < 0.05$; **The difference with the group of minimal risk is significant (0. 1–7 sSV), $p < 0.01$. SATI: Summarized aggregation time index, SFMC: Soluble fibrin monomer complex.

have showed the significant increase in aggregation time index (ATI), summarized ATI in comparison with the patients from the minimal radiation risk zone ($p < 0.05$). There were no significant differences in fibrinogen concentration by the corresponding groups of radiation exposure. There was a significant decrease in rifampicin induced activation of platelets (RIA) in stroke patients living in extremely high radiation zone. There was no significant difference found in the level of ATIII by zone of radiation exposure.

The study of coagulation hemostasis had revealed the significant increase in fibrinogen concentration in patients from extremely high radiation zone: 4.7 ± 0.14% against 3.2 ± 0.11%, in patients living in minimal radiation risk zone ($p < 0.01$). The patients from extremely high radiation risk had significant decrease in fibrinolysis time in comparison to patients from minimal radiation risk ($p < 0.05$). There was a significant increase in plasma concentration of soluble fibrin monomer complex (SFMC) found in patients living in extremely high radiation zone in comparison to patients, living in minimal radiation exposure ($p < 0.05$).

The next step of the study was to evaluate frequency of antiphospholipid syndrome (APS) distribution in stroke patients by zones of radiation risk. The primary APS was diagnosed in 24 (6.7%) patients in total group of stroke patients (11 males and 13 females), from which 21 patients with ischemic stroke and 3 with hemorrhagic stroke.

The distribution of stroke patients with antiphospholipid syndrome by zones of radiation risk. The 41.6% of stroke patients with AFS lived in high radiation risk zone, 50% of patients in extremely high and maximal radiation risk zones, representing significantly higher frequency of APS in stroke patients in comparison to the patients with minimal radiation exposure (2.7%), ($p < 0.05$).

The resistance to activated protein C (Va Leiden defect) was found in 28 (10.6%) of ischemic stroke patients and 8 (8.5%) hemorrhagic stroke patients. The deficiency in protein C was found in 8 (3%) ischemic stroke and 3 (3.2%) hemorrhagic stroke patients; the deficiency in protein S in 3 (1.1%) ischemic stroke and not found in hemorrhagic stroke.

The next step was to find the frequency of genetic thrombophilia's in the stroke patients. The patients with the most common genetic thrombophilia's were relatively young age (the average age 38.2 ± 1.2 years), and therefore, the representatives of second and third generation of exposed cohort.

In Table 2 shows the frequency of genetic thrombophilias in stroke patients by zones of radioactive risk. The significant majority of patients with genetic thrombophilias lived in the area with high radiation risk: (14.5%) in high radiation risk zone, 17.5% in maximal radiation risk zone and 16.9% in extremely high radiation risk zone, against 6.9% in minimal radiation zone. The frequency of the most common genetic thrombophilias in general cohort of stroke patients was 14%.

Table 2: Distribution of patients with thrombophilia by zone of radiation exposure

Genetic thrombophilia's	Zones of radiation exposure risk (abs.(%))			
	100–448 sSV, (n = 53)	35–100aSV, (n = 74)	7–35 sSV, (n = 158)	0.1–7 sSV (n = 72)
Leiden Va defect	7 (13.2%)	9 (13.5%)	15 (9.4%)	5 (6.9%)
Protein C deficit	3 (3.7%)	3 (4%)	6 (3.7%)	0
Protein C deficit	0	1 (1.3%)	2 (1.2%)	0
Total: 50 (14.0%)	9 (16.9%)	13 (17.5%)	23 (14.5%)	5 (6.9%)

Presence of significantly higher frequencies of genetic thrombophilias in the areas with higher radiation risk points out on modifying influence of radiation factor on the occurrence of genetic hemostatic anomalies. Leiden Va defect was found significantly more often in patients lived in high radiation risk zone (9.4%), in 13.5% stroke patients from maximal radiation risk, in 13.2% patients lived in extremely high radiation risk, in comparison to 6.9% patients lived in minimal radiation risk zone. The frequency of Leiden Va defect in general cohort of stroke patients comprised 10.0%, which points out on the presence of modifying role of radiation factor on the frequency of Leiden Va defect.

The analysis of homocysteine concentration in stroke patients by radiation risk zones was done on 142 stroke patients (82 males and 60 females), 110 of ischemic stroke and 32 patients with hemorrhagic stroke. The distribution of the patients by the zones of radiation exposure is presented in Table 3.

Table 3: The concentration of plasma homocysteine in stroke patients by zones of radiation exposure risk

Homocysteine concentration	Zones of radiation exposure risk			
	100–448 sSV, (n = 22)	35–100 sSV, (n = 34)	7–35 sSV, (n = 68)	0.1–7 PSV (n = 31)
mkg/ml	14.34–£1.22	12.3i–0.64*	11.9+0.73*	8.9–£0.78

*The differences with the data with minimal radiation risk significant (0.1–7 sSV) $p < 0.05$. **The differences with the data with minimal risk are significant 0.1–7 sSV), $p < 0.01$; × the differences between zone with maximal and extremely high radiation risk are significant, $p < 0.05$.

As at is seen from Table 3, the patients from zone with extremely high radiation risk had significantly higher level of plasma homocysteine in comparison to patients from other zones, ($p < 0.01$). Furthermore, the significantly higher levels of plasma homocysteine were found in the group with maximal and high radiation exposure, in comparison to the group of patients from minimal risk zone ($p < 0.05$).

Analysis of levels of plasma lipoprotein A by zones of radiation risk was done in 127 stroke patients, as presented. In patients who lived in the territory with radiation dose higher than 35 sSV, had significantly higher concentrations of lp (a) in comparison to stroke patients, who lived in the area with minimal radiation risk, $p < 0.05$.

Discussion

One the main environmental factor, influencing the health of the population of Eastern region of Kazakhstan is the existence of former Semipalatinsk testing polygon.

The study of hemostasis in stroke patients by zones of radiation risk has revealed the significant increase in aggregation activity of platelets, fibrinogen concentration, slowing the fibrinolysis and increase in SFMC, in patients living in extremely high radiation risk zone, and therefore the presence of more active processes of thrombi generation in the corresponding group of patients. As per Mikhailidis *et al*. [21] the increase in fibrinogen content is considered to be one of the predictors of vascular thrombosis in ischemic heart disease even among healthy individuals. Therefore, the significant increase in plasma fibrinogen concentration in stroke patients residing in the area with higher than baseline radiation risk has to be taken into consideration when the disease prognosis is determined.

Analysis of the frequencies of the distribution of AFS in stroke patients has showed the higher frequencies of AFS among stroke patients living in extremely high and high radiation risk zones. Considering the importance of AFS in trombogenesis and development of stroke at younger age, we think that this phenomenon needs more close investigation.

The analysis of the frequency of antiphospholipid syndrome and genetic thrombophilic states (Leiden Va defect, protein C and S deficit) in stroke patients lived in the zone has revealed their significantly high distribution in the areas with radiation dose higher than 35 cSV. In contrast, the deficits of protein C and S were not found in stroke patients living in the areas with minimal radiation exposure, while were present in stroke patients lived in zones with extremely high, maximal, and high radiation risk.

In patients from extremely high and maximal radiation risk the more prominent changes in the concentration of plasma homocysteine was discovered, as well as higher concentration of lp (a) in comparison to patients who lived in the area with minimal radiation risk, $p < 0.05$. The increase in plasma concentration of lp (a), therefore their deposition in the artery walls of heart and brain in stroke patients, lived in the area with high radiation risk, shows the presence of more intense processes of arteriosclerosis in this group of patients.

The results of our study point out on the presence of modifying influence of low radiation dosages on pathophysiological mechanisms of stroke progression of stroke in the region. As it was mentioned before, the found pathological changes at low doses of radiation on cardiovascular system are stenosis and occlusion of large arteries [22].

Increase of plasma lp (a) concentration, and therefore its increased accumulation (deposition) in the artery wall in heart and brain of stroke patients, who lived in the area with increased radiation risk points out to more intensive processes of atherothrombosis in this group patients.

Conclusion

Summarizing the results of conducted analysis, we can see the presence of indirect evidences of modifying influence of radiation factor on pathogenic mechanisms of stroke in Eastern region of Kazakhstan.

References

1. Shimizu Y, Kodama K, Nishi N, Kasagi F, Suyama A, Soda M, *et al*. Radiation exposure and circulatory disease risk: Hiroshima and nagasaki atomic bomb survivor data, 1950-2003. BMJ. 2010;340:b5349. https://doi.org/10.1136/bmj.b5349
PMid:20075151
2. Preston DL, Pierce DA, Shimizu Y, Cullings HM, Fujita S, Funamoto S, *et al*. Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. Radiat Res. 2004;162(4):377-89. https://doi.org/10.1667/rr3232
PMid:15447045
3. Little MP, Tawn EJ, Tzoulaki I, Paris F, Tapio S, Elliott P, *et al*. Review and meta-analysis of epidemiological associations between low/moderate doses of ionizing radiation and circulatory disease risks, and their possible mechanisms. Radiat Environ Biophys. 2010;49(2):139-53. https://doi.org/10.1007/s00411-009-0250-z
PMid:19862545
4. Shimizu Y, Pierce DA, Preston DL, Mabuchi K. Studies of the mortality of atomic bomb survivors. Report 12, Part II. Noncancer mortality: 1950-1990. Radiat Res. 1999;152(4):374-89.
PMid:10477914
5. Cullings HM. Impact on the Japanese atomic bomb survivors of radiation received from the bombs. Health Phys. 2014;106(2):281-293. https://doi.org/10.1097/HP.0000000000000009
6. Wang Y, Boerma M, Zhou D. Ionizing radiation-induced endothelial cell senescence and cardiovascular diseases. Radiat Res. 2016;186(2):153-61. https://doi.org/10.1667/RR14445.1

PMid:27387862

7. Donato AJ, Morgan RG, Walker AE, Lesniewski LA. Cellular and molecular biology of aging endothelial cells. J Mol Cell Cardiol. 2015;89(Pt B):122-35. https://doi.org/10.1016/j.yjmcc.2015.01.021

PMid:25655936

8. Sermsathanasawadi N, Ishii H, Igarashi K, Miura M, Yoshida M, Inoue Y, *et al*. Enhanced adhesion of early endothelial progenitor cells to radiation-induced senescence-like vascular endothelial cells *in vitro*. J Radiat Res. 2009;50(4):469-75. https://doi.org/10.1269/jrr.09036

PMid:19628926

9. Lowe D, Raj K. Premature aging induced by radiation exhibits pro-atherosclerotic effects mediated by epigenetic activation of CD44 expression. Aging Cell. 2014;13(5):900-10. https://doi.org/10.1111/acel.12253

PMid:25059316

10. Geider H, Pawar SA, Kerschen EJ, Nattamai KJ, Hernandez I, Liang HP. *et al*. Pharmacological targeting of the thrombomodulin-activated Protein C pathway mitigates radiation toxicity. Nat Med. 2012;18(7):1123-9. https://doi.org/10.1038/nm.2813

PMid:22729286

11. Higashi Y, Kihara Y, Noma K. Endothelial dysfunction and hypertension in aging. Hypertens Res. 2012;35(11):1039-47. https://doi.org/10.1038/hr.2012.138

PMid:22972557

12. Borghini A, Gianicolo EA, Picano E, Andreassi MG. Ionizing radiation and atherosclerosis: Current knowledge and future challenges. Atheroslerosis. 2013;230(1):40-7. https://doi.org/10.1016/j.atherosclerosis.2013.06.010

PMid:23958250

13. Sasaki H, Wong FL, Yamada M, Kodama K. The effects of aging and radiation exposure on blood pressure levels of atomic bomb survivors. J Clin Epidemiol. 2002;55(10):974-81. https://doi.org/10.1016/s0895-4356(02)00439-0

PMid:12464373

14. Kallfass E, Kraemling HJ, Schultz-Hector S. Early inflammatory reaction of the rabbit coeliac artery wall after combined intraoperative (IORT) and external (ERT) irradiation. Radiother Oncol. 1996;39(2):167-78. https://doi.org/10.1016/0167-8140(96)01708-2

PMid:8735484

15. Fajardo LF. Basic mechanisms and general morphology of radiation injury. Semin Roentgenol. 1993;28(4):297-302. https://doi.org/10.1016/s0037-198x(05)80091-4

PMid:8272878

16. Zidar N, Ferluga D. Hvala A. Popovic M. Soba E. Contribution to the pathogenesis of radiation-induced injury to large arteries. J Laryngol Otol. 1997;111(10):988-90. https://doi.org/10.1017/s0022215100139167

PMid:9425496

17. Ibraev SS. Complex Estimation of the Health State of People Living at the Area Adjacent to Semipalatinsk Polygon and Exposed to Low Doses of Radiation: Avtoreph of the Candidate of Medical Science. Southeastern Kazakhstan: Alma Ata; 1992. p. 33.

18. Ibraev NS. The Influence of Radioactive Testing at Semipalatinsk Polygon on Health of the Population of Some Regions of the Oblast: Aftoreph of the Dissertation the Candidate of Medical Science. Northeast Kazakhstan: Semipalatinsk; 1995. p. 26.

19. Grosche B, Zhunussova T, Apsalikov K, Kesminiene A. Studies of Health Effects from Nuclear Testing near the Semipalatinsk Nuclear Test Site, Kazakhstan. Cent Asian J Glob Health. 2015;4(1):127. https://doi.org/10.5195/cajgh.2015.127

20. Grosche B, Simon SL, Apsalikov KN, Pivina LM, Bauer S, Gusev BI, *et al* Mortality from cardiovascular diseases in the Semipalatinsk historical cohort, 1960-1999, and its relationship to radiation exposure. Radiat Res. 2011;176(5):660-9. https://doi.org/10.1667/rr2211.1

PMid:21787182

21. Mikhailidis DP, Spyropoulos KA, Ganotakis ES. Fibrinogen and lipoprotein (a): Associations in a population attending a cardiovascular risk clinic and effect of treatment with ciprofibrate. Fibrinolysis. 1996;10(Suppl):17.

22. Neuber C, Pufe J, Pietzsch J. Influence of irradiation on release