INTELLIGENCE DETERIORATION FOLLOWING ACUTE RADIATION SICKNESS

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Abstract

Objective: Cognitive impairment in the remote period of Acute Radiation Sickness (ARS) is an expected outcome. This study was performed to examine the contribution of irradiation on intelligence deterioration.

Method: 14–15 years after the Chernobyl accident, a cross-sectional IQ-study on ARS-patients (n=29) and normal controls (n=24) was done. Verbal (VIQ), Performance (PIQ) and Full (FIQ) IQs were assessed by the adapted version of the Wechsler Adult Intelligence Scale (WAIS). Pre-exposure IQ was estimated by the regression equation developed by Dr. Beilin Gao (China).

Results: VIQ and FIQ scores were lower in ARS-patients than in controls (M±SD: 103.2±13.5 vs 113.8±9.4, and 102.2±11.4 vs 110.2±8.6, correspondingly). Radiation dose of 1 Gy decreases FIQ of 4.1–6 scores at a dose range of 1–3.8 Gy. A reduction of 1 point of FIQ could be a result of exposure to 0.17–0.24 Gy. Discrepancy between pre-exposure and actual IQ (M±SD) in ARS-patients is dramatically severe as compared to controls: VIQ - 15.8±14.4 vs 2.3±4.5, PIQ - 14.2±10.8 vs 8.7±3.5, and 16.8±12.7 vs 5.9±2.6, correspondingly.

Conclusions: According to pre-exposure IQ estimations, IQ deterioration in ARS-patients, especially, in verbal and full intelligence, was observed. Such cognitive impairment could be evidence of a brain organic syndrome with an important involvement of the left dominant hemisphere, in the remote period of ARS.

Key words: Chernobyl accident, cognitive impairment, intelligence, pre-exposure IQ, ionizing radiation, Acute Radiation Sickness

Declaration of interest: none

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Introduction

The primary radiation CNS damage was assumed to be the result of total body exposure to ionizing radiation at doses higher than 100 Gy (the cerebral form of Acute Radiation Sickness [ARS]). Secondary radiation CNS damage was set at radiation doses of 50–100 Gy (the toxemic form of ARS) (Gus’kova and Bisogolov 1971).

The most conservative threshold of radiation-induced neuroanatomic changes was assumed to be 2–4 Gy for whole body irradiation, while that for the CNS was assumed to be 50–100 Gy (Gus’kova and Shakirova 1989, Gus’kova 2007). The radiotherapeutic tolerable dose for the brain was assumed to be 55–65 Gy, and the tolerable fractional dose was assumed to be 2 Gy (Mettler and Upton 1995).

Crucial long-term neurotoxicity of brain radiotherapy is cognitive dysfunction till to dementia, as a consequence of leukoencephalopathy and brain atrophy (Schlegel et al. 1999, Chang and Maor 2003). Brain exposure to the median radiation dose 60 Gy (range 50–68 Gy) in fractions of 1.8 to 2 Gy resulted in memory impairment (80%), difficulties with visual-motor speed, frontal lobe executive functions, and fine motor coordination, as well as brain necrosis with consequential dementia and blindness, brain atrophy, pituitary dysfunction. Neurocognitive symptoms were related to the total dose of radiation (Meyers et al. 2000).

In the Adult Health Study (a prospective cohort study begun in 1958) in Hiroshima, Japan, atomic bomb radiation dose did not show any significant association with vascular dementia or Alzheimer’s disease detected 25 to 30 years later. Risk factors for dementia were age, higher systolic blood pressure, history of stroke, history of hypertension, history of head trauma, lower milk intake, and lower education (Yamada et al. 1999, 2003). However, taking into account that an increased blood pressure was the main contributor to vascular dementia (Yamada et al. 1999), it is important that at the same Adult Health Study it was recently found the statistically significant effect of ionizing radiation on the longitudinal trends of both systolic and diastolic blood pressure. This phenomenon is compatible with the degenerative effect of ionizing radiation on blood vessels (Sasaki et al. 2002).

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In 50–60th, nearly 20,000 Israel children were exposed to X-ray irradiation on head for ringworm (*tinea capitis*) management. Doses on brain constituted ~1.3 Gy only, but even such exposure resulted in an increased trend of brain damage in 20 years. Lower school progress, deterioration of IQ, some psychological tests indices, lesser number of graduate school years, and increased risk of mental disorders were observed (Ron et al. 1982).

The verbal scores at the Scholastic Aptitude Test (SAT) in the USA, years 1958-1982, were related to the nuclear weapons tests at the times of birth of the subjects tested 18 years earlier. The deteriorating level of verbal IQ was found associated with open air nuclear testing. The drop in IQ was greatest in Nevada and New Mexico (Graeub 1994).

Immediately after the Chernobyl accident (April 26, 1986), autonomic (vegetative) vascular dystonia (VVD) and neurotic disorders were observed: at 0.8–2.1 Gy — mild ARS (or ARS of the 1st severity degree); at 2–4 Gy — moderate ARS (or ARS of the 2nd severity degree) causing VVD; at 4.2–6.3 Gy — severe ARS (or ARS of the 3rd severity degree) causing acute radiation and radiation-toxic encephalopathy, acute psychosis with visual and acoustical hallucinations, and brain edema; at 6–16 Gy — very severe to lethal ARS (or ARS of the 4th severity degree) causing acute radiation and radiation-toxic encephalopathy, subarachnoidal-parenchimatous hemorrhage, acute brain edema, and swelling (Torubarov et al. 1989).

No clear signs of organic brain damage were registered during the first 3 years after irradiation in ARS survivors; however, mental working capacity deterioration and asthenisation were in proportion to the severity of ARS. Further, progressive structural-functional brain damage — post radiation encephalopathy or post radiation organic brain syndrome — was revealed in the remote period of ARS according to neuropsychiatric follow-up studies (Nyagu et al. 1997, 1999, 2002). Neurophysiological biomarkers (Loganovsky and Yuryev 2001, 2004), and neuropsychological (Antipchuk 2003), neuroimaging (Bomko 2004) and dopplerographic (Denisyuk 2006) peculiarities of post radiation brain damage at the remote period of ARS were found.

At present, in spite of classical radiological point of view regarding an "extremely radioresistancy" of the CNS, the evidence is dramatically increasing in support of the CNS radiosensitivity. The current opinions on the pathogenesis of radiation brain damage following exposure even to low doses of ionizing radiation includes: disrupted neurogenesis in the adult hippocampus (Andres-Mach et al. 2008, Kim et al. 2008), changes in the gene expression profile (Yin et al. 2003, Lowe et al. 2009), a neuroinflammatory response, neurosignaling alterations, apoptotic cell death, cell death and injury mediated by secondary damage, etc., together with the well-known role of the "glial-vascular union". Thus, exposure to radiation has multiple effects on the brain, behavior and cognitive functions. These changes depend largely on the radiation dose (Wong and Van der Kogel 2004, Gourmelon et al. 2005, Loganovsky 2009, Marazziti et al. 2012, Picano et al. 2012).

Radiation cognitive impairment is a paramount neuropsychiatric effect (Britten et al. 2012). The delayed consequences of radiation damage on learning and memory suggest that although high dose irradiation-induced white matter necrosis is associated with substantial impairment, cognitive deficits may also be detected after a lower dose, not associated with the development of necrosis (Hodges et al. 1998). Thus, an intellectual deterioration following ARS is a quite expected outcome. However, in practice, it is often difficult to make a confident measure of intellectual impairment after radiation brain damage.

In the clinical practice, the conventional identification of intellectual impairment from brain damage is based mainly on a post-injury intelligence level. A diagnosis of intellectual impairment is considered if post-injury IQ scores are less than 70 and there is no malingering and no preexisting mental retardation. This approach does not take into consideration individual differences in pre-injury IQ levels (Gao et al. 2000). Taking into account that the ARS-patients following the Chernobyl accident are the persons with above the average educational and professional level (Nuclear Power Plant personnel, firemen, etc) (UNSCEAR 2000), the definition of post radiation intelligence deterioration as IQ<70 scores is inapplicable. Obviously, a «normal» post radiation IQ = 100 for an ARS-patient could be an intelligence deterioration of more than one standard deviation (15 points).

Estimation of premorbid IQ in brain injury is clinically and scientifically valuable because it permits the quantification of the cognitive impact of injury (Schretlen et al. 2005, Green et al. 2008). Methods used to estimate premorbid cognitive functioning are based on demographic information, combined current test performance with demographics, and current reading (word recognition) ability (Baade and Schoenberg, 2004). There are several test for assessment of premorbid IQ − the Wechsler Test of Adult Reading (WTAR), the National Adult Reading Test (NART), achievement measures from school records, etc. (Bright et al. 2002, Mackinnon and Mulligan, 2005, Green et al. 2008). All these approaches have drawbacks, including difficulty estimating premorbid abilities of people close to the extremes of intellectual functioning (i.e., estimating the premorbid ability of individuals in the high or borderline intellectual ranges) (Baade and Schoenberg, 2004).

A number of linear regression equations for the estimation of premorbid IQ from demographic variables were proposed (Barona et al. 1984, Kufman et al. 1988, Graves 2000, Gao et al. 2000). Demographic-based regression equations can provide unbiased and useful estimates of premorbid IQ (Crawford et al. 2001). However, it was noted the limited accuracy of regression-based estimates of premorbid IQ (Basso et al. 2000, Veiel and Koopman 2001) and discrepancy between predicted and obtained Wechsler Adult Intelligence Scale-Revised (WAIS-R IQ) scores (Demakis et al. 2001). In spite of this criticism, it seems that the regression-based estimates of premorbid IQ from demographic variables is the best way for estimation of intellectual impairment following accidental over irradiation, when any psychometrical information before the exposure is not available.

The aim of the study was to explore the post radiation cognitive impairment in the ARS-survivors following the Chernobyl accident using the intelligence deterioration assessment with regression-based estimates of premorbid (pre-exposure) IQ.

Subjects and Methods

Subjects

During 2000–2001 (14 to 15 years after irradiation) a cross-sectional IQ-study on ARS-patients (n=29) and external normal controls (n=24) was carried out. The ARS-patients and controls were recruited from the register of the State Institution "National Research Centre for Radiation Medicine of National Academy of Medical Sciences of Ukraine", Kiev. All participants were examined in the Department of Radiation Psychoneurology of the Institution. All ARS-patients are under the life span follow up study at the Centre with annual medical examinations.

In order to control the influences of traditional risk factors that could affect the IQ pattern, we selected those ARS-patients who met the inclusion criteria as follows: 1) age at the moment of examination <60 years; 2) males; 3) absence of any neuropsychiatric and physical disease or head trauma before the accident; 4) absence of head trauma, stroke, neuroinfections and dependence on any psychoactive substances (other than tobacco) after the accident (on the base of follow up study); 5) right-handedness.

The ARS-patients have been exposed to ionizing radiation at the most dramatic period of the Chernobyl disaster — the night of the accident (April 26, 1986). The ARS- and control groups have no differences in age. They had a pretty high professional and educational level; they were mainly firemen and personnel of the power station. The controls have similar socio-demographical, occupational, economical and educational level (**table 1**).

The ARS group includes 29 patients exposed in 1986 to acute ionizing irradiation in dose range 1–3.8 Gy (M=1.85; SD=0.61; Median=1.76 Gy). Among them there were 25 patients who had mild ARS or ARS of the 1st severity degree (dose absorbed 1–2 Gy), 4 — moderate ARS or ARS of the 2nd severity degree (2–3.8 Gy).

The evaluator cannot be "blind" to the participants' conditions (ARS or control) due to the unique specificity of the ARS-patients. Compliance of the ARS-patients of mild to moderate ARS was pretty high (72%), however those exposed to higher doses (>4 Gy) declined the testing due to severe fatigue.

In 1986, all ARS patients were diagnosed for VVD (autonomous nervous system dysfunction or dysautonomia) that refers to etiologically heterogeneous abnormalities of diencephalic-limbic-reticular complex. In 3–5 years after exposure, neuropsychiatric symptoms became more severe and these patients were diagnosed for «dyscirculatory encephalopathy», i.e. chronic cerebrovascular disorder. However, signs of proper vascular diseases (arterial hypertension, cerebral atherosclerosis, etc.) were observed in 35% of them only. Further, neuropsychiatric syndrome in patients at the remote period of ARS was classified as «post radiation encephalopathy», which we proposed as a new ICD-10 diagnostic category F07.3 «Post radiation organic syndrome». «Post radiation organic syndrome» was classified within the frame of the ICD-10 F07 «Personality and behavioral disorders due to brain disease, damage and dysfunction», which also corresponds to the DSM-IV 310.1 «Personality change due to general medical condition (ARS)» (Nyagu et al. 1997, 1999, 2002; Loganovsky and Yuryev 2001, 2004).

Methods

Verbal (VIQ), Performance (PIQ) and Full IQs (FIQ) for both patients and controls were obtained by the adapted version for Russian population of the Wechsler Adult Intelligence Scale (WAIS) (Phylimonenko and Tymopheyev 1995, Wechsler 1997).

One of the most important methodological limitations of the studies on neuropsychiatric disorders after accidental overexposure is an absence of validated data on pre exposure conditions. In this study we solved this methodological issue by: 1) retrospective estimation of health conditions before the accident (inclusion criteria — healthy before exposure), and 2) pre-exposure IQ estimation with the regression equation kindly provided by Dr. Beilin Gao, M.D., Ph.D., Department of Forensic Psychiatry, Shenzhen Kangning Hospital and Mental Health Institute, Guangdong, China) (Gao et al. 2000). Premorbid IQ estimation is still a difficult problem in neuropsychiatry and this has a special significance in examination of intelligence deterioration following brain damage (Hartlage 1997).

The regression equation for an estimation of pre-injury IQ on WAIS by Gao is as follows:

Table 1. *Descriptive characteristic of ARS-patients and controls*

Characteristic	ARS-patients (n=29)	t, χ^2, Fisher exact P	P	Controls (n=24)
Age (M±SD)	43.1±5.1	–0.9	0.4	44.2±4.3
Years of education (M±SD)	12.9±1.9	0.7	0.5	12.4±2.5
Educational level:				
Primary school	1 (3.4%)	0.4		2 (8.3%)
Secondary school	20 (69.0%)	0.7	0.4	19 (79.2%)
University	8 (27.6%)	0.1		3 (12.5%)
Occupational level:				
Worker, operators	8 (27.6%)	0.3		4 (16.7%)
Specialist (engineer, fireman, etc)	21 (72.4%)	0.9	0.3	20 (83.3%)

Pre-IQ = C + ACo·Age + OCo·O + SCo·Sex + ECo·Edu

Where «C» is constant; «Co» — coefficient; «ACo» — age coefficient; «OCo» — occupation coefficient; «SCo» — sex coefficient; «ECo» — education coefficient.

Moreover, «Age» and «Education» in this equation are not actual number but a quantifying value. At different ages, different values are considered: 16–17 years old = 1; 18–19 = 2; 20–24 = 3; 25–35 = 4; 35–44 = 5; 45–54 = 6; 55–64 = 7; more than 65 = 8. The different education also has different values: illiteracy = 1; primary school = 2; middle school = 3; high school = 4; college and higher = 5. Sex: female = 1; male = 2. Occupation quantifies values: server = 1; farmer = 2; worker = 3; civil servant = 4; student = 5; teacher, technician and scientist =6.

There are different coefficients to calculate pre-exposure VIQ, PIQ, and FIQ, presented in **table 2**. This **table** lists the constants, different coefficients, and double relative coefficients (R^2). «R^2» means the relativity between pre-IQ and actual IQ. Statistical analysis was performed using STATISTICA and MS EXCEL software.

Results and Discussion

Mean VIQ, PIQ, and FIQ in the ARS-patients and controls are within the range of "normal" intelligence. However, as shown in **table 3**, VIQ and FIQ are lower in ARS-patients than in controls.

IQs of the ARS-patients were compared also with population data (n=193) (O'Leary et al. 2000). As it is shown in **table 4**, VIQ, PIQ, and FIQ in the remote period of ARS were lower of 7.7; 12 and 10.9 points as compared to population scores (O'Leary et al. 2000).

If we assume that IQ deterioration in the ARS-patient is the radiation effect, we can calculate IQ deterioration per dose of 1 Gy at the dose range 1–3.8 Gy of acute whole body irradiation as shown in **table 5**. According to own controls or normative population data, a dose of 1 Gy could result in a FIQ deterioration of 4.1–6 points. Obviously, it is very difficult to clinically estimate such IQ reduction in subjects with a medium-high pre-morbid IQ. Only in low pre-morbid IQ subjects, irradiation of 1–3.8 Gy could be recognized as a significant cognitive deficit (dementia).

From these calculations, we can estimate the dose of total whole body acute exposure that could result in an IQ reduction of 1 point, as shown in **table 6**. One-point FIQ reduction could be the result of a 0.17–0.24 Gy exposure.

Interpretation of the estimates of IQ radiation-induced deterioration in patients who were diagnosed with ARS requires a number of assumption and to consider some limitations. First of all, we cannot assess IQ in the ARS-patients who had the most severe ARS due to their exclusive exhaustion. Second, the group of ARS-patients for whom IQ was assessed is small. However, to our knowledge, this is the first attempt to investigate IQ related to units of absorbed radiation dose, at dose range 1–3.8 Gy, in the remote period of acute whole body irradiation.

Third, our estimates are based on both comparison with controls and population data. At the same time we cannot exclude an impact of trans-cultural factors on IQ. Probably, this could explain why, in the remote period of ARS, VIQ was more deteriorated in ARS patients as compared to controls, whilst also PIQ when ARS patients compared to normative data. It should be noted that in the remote period following cranial radiotherapy, a reduction of VIQ was observed in other studies (Copeland et al. 1999, Armstrong et al. 2000, Cheung et al. 2000, Kieffer-Renaux et al. 2000).

The assumption that IQ deterioration in ARS-patients is the result of radiation may be criticized. There are alternative explanations: age; physical diseases; non-radiation risk factors; low baseline IQ. However, subjects included in the study were relatively young (34–51 years old; WAIS is standardized on age, and age did not influence IQ (F=0.6; P=0.78). All subjects were healthy before the accident and none had severe physical disease (stroke, vascular dementia, multyinfarct dementia, etc) that could explain IQ reducing. The diagnosed somatic or neurological pathology did not influence IQ (F=0.9; P=0.43 and F=0.005; P=0.94 correspondingly). There were no alcohol abusers, and mild to moderate alcohol intake, as well as tobacco smoking, did not influence IQ (F=0.04; P<0.08).

Taking into account the high educational and occupational baseline level in the ARS-patients and their lower mean IQ as compared to controls, it is reasonable to hypothesize intelligence deterioration in ARS patients. This hypothesis was supported by pre-exposure IQ comparison. As it is shown in **table 7**, there was no difference in pre-exposure VIQ, PIQ, and FIQ between ARS- and control subjects.

On the other hand, significant differences between pre-IQ and actual IQ in ARS-patients as compared to controls were observed, as shown in **table 8**. Therefore, in the remote period, VIQ, PIQ, and FIQ can be

Table 2. *Constants, coefficients, and R^2 for pre-exposure IQs calculating (by Gao)*

Index	Verbal pre-IQ	Performance pre-IQ	Full pre-IQ
Constant (C)	58.8	66.9	59.5
Age coefficient (ACo)	1.09	0.92	1.1
Occupation coefficient (OCo)	2.1	1.46	2.01
Sex coefficient (SCo)	4.48	3.03	4.13
Education coefficient (Eco)	7.37	6.34	7.45
Relativity between pre-IQ and actual IQ (R^2)	0.633	0.511	0.625

Table 3. *Mean IQs (M±SD) in ARS-patients and controls*

IQ (WAIS)	ARS-patients	t	P	Controls
Verbal	103.2±13.5	–3.3	<0.002	113.8±9.4
Performance	100.9±9.5	–1.3	<0.2	104.9±7.9
Full	102.2±11.4	–2.8	<0.007	110.2±8.6

Table 4. *Mean IQs (M±SD) in ARS-patients and normative literature data (O'Leary et al. 2000)*

IQ (WAIS)	ARS-patients	t	P	Population
Verbal	103.2±13.5	–3.56	<0.001	110.9±13.1
Performance	100.9±9.5	–7.35	<0.001	112.9±12.3
Full	102.2±11.4	–5.8	<0.001	113.1±12.6

Table 5. *Assessment of IQ deterioration per 1 Gy at dose range 1–3.8 Gy*

IQ (WAIS)	Control (n=24)	Population (n=193) (O'Leary et al. 2000)
Verbal	5.9	4.2
Performance	1.7	6.6
Full	4.1	6

Table 6. *Assessment of Radiation Dose Reducing IQ of 1 point*

IQ (WAIS)	Control (n=24)	Population (n=193) (O'Leary et al. 2000)
Verbal	0.17	0.24
Performance	0.59	0.15
Full	0.24	0.17

Table 7. *Mean pre-exposure IQs (M±SD) in ARS-patients and controls*

Pre-IQ	ARS-patients	t	P	Controls
Pre-Verbal	118.4±8.6	0.98	>0.05	116.2±10.1
Pre-Performance	114.6±7	0.99	>0.05	112.8±8.2
Pre-Full	118.4±8.6	0.98	>0.05	116.1±10.1

Table 8. *Differences between pre-exposure and actual IQ (M±SD) in ARS-patients and controls*

IQ	ARS-patients	t	P	Controls
Verbal	15.8±14.4	4.4	<0.001	2.3±4.5
Performance	14.2±10.8	2.4	<0.02	8.7±3.5
Full	16.8±12.7	4.1	<0.001	5.9±2.6

Table 9. *Correlation matrix of pre-exposure and actual IQ (r, P) in ARS-patients and controls*

Pre-IQ	**Actual IQ**					
	Verbal		Performance		Full	
	ARS-patients	Controls	ARS-patients	Controls	ARS-patients	Controls
Pre-Verbal	r=0.19 P=0.32	**r=0.89 P<0.001**	r=0.16 P=0.41	**r=0.90 P<0.001**	r=0.19 P=0.31	**r=0.97 P<0.001**
Pre-Performance	r=0.19 P=0.30	**r=0.89 P<0.001**	r=0.15 P=0.43	**r=0.90 P<0.001**	r=0.19 P=0.31	**r=0.97 P<0.001**
Pre-Full	r=0.19 P=0.31	**r=0.89 P<0.001**	r=0.16 P=0.42	**r=0.90 P<0.001**	r=0.19 P=0.31	**r=0.97 P<0.001**

assumed as significantly deteriorated in comparison with pre-exposure IQ, according to the model by Gao.

We found empirical evidence in support of the Gao regression model for the estimation of pre-IQ as shown in **table 9**. In non-exposed controls, the linear correlations of pre-exposure and actual IQs are very high and strong, while in ARS-patients such correlations are weak. This may be explained by post radiation cognitive impairment.

The Gao regression model for the estimation of pre-IQ has been validated in Ukrainian controls, and this method seems to be pretty accurate and sensitive for estimation of post radiation cognitive deficit.

The estimations of pre-exposure IQ in ARS-patients are rather high (114-118). This could be reasonable explained by high educational and professional level of ARS-survivors (atomic energy specialists, firemen officers, etc).

We tried to control the influence of confounders on cognitive impairment by inclusion/exclusion criteria and social-demographic-matched control group. In particular, we controlled for traditional risk factors of cognitive factors (age, physical and neuropsychiatric diseases, injuries, infections, alcohol and drug abuse, etc). However, we were unable to eliminate the effect of psychological impact of having experienced ARS. However, it is unlikely that ARS-patients had developed very severe stress-related disorders, since these subjects were professionals, prepared to radiation emergencies.

In conclusion, taking into account the abovementioned limitations, we here hypothesized post radiation cognitive impairment in the delayed period of ARS as a result of the Chernobyl accident. According to pre-exposure IQ estimations, the IQ deterioration in the ARS-patients is 2-3 times higher than in the controls. IQ deterioration in controls was not significant (less than one SD=15 for the WAIS), whilst in the ARS-patients the IQ-deterioration was quite relevant since higher than one SD. Predominant deterioration of verbal IQ following radiation exposure has a particular interest. Low verbal and full IQ scores as compared to controls, as well as IQ deterioration according to pre-exposure IQ estimation suggest a brain organic syndrome, with a relevant involvement of the left, dominant hemisphere in the remote period of ARS.

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