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SHORT COMMUNICATION

Radiation Effects on Late-life Neurocognitive Function in Childhood Atomic Bomb Survivors: A Radiation Effects Research Foundation Adult Health Study

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High-dose radiation in childhood such as is used in radiation therapy causes cognitive decline, but there is insufficient research on the cognitive effects of low- to medium-dose radiation. We aimed to reveal the association between atomic bomb radiation exposure in childhood and late-life neurocognitive function. In 2011 and 2013, we mailed the Neurocognitive Questionnaire (NCQ) to subjects who were 12 years old or younger at the time of the atomic bombing. We converted the four NCQ subscales (metacognition, emotional regulation, motivation/organization, and processing speed) to T scores and defined the highest 10% of the controls (exposure dose $<$ 5 mGy) as impaired. We used a generalized linear mixed model to evaluate the effect of radiation exposure on T scores and percentage impaired. We enrolled 859 participants. At the time of the bombing, the mean (SD) age was 6.7 (3.8) years for the control (N $=$ 390) and 6.1 (3.8) years for the exposed (N $=$ 469). At the time of replying to the questionnaire, the mean age of all the participants was 73.7 (3.8) years of age. After adjusting for cofactors, older age was related to the decline of all neurocognitive subscales. Sex and education level had relevance to some of the subscales. For neurocognitive function, exposure dose was not related except to percentage impaired, motivation/organization. Late-life neurocognitive function in atomic bomb survivors exposed as children was associated with age, but not clearly with radiation dose. More studies are needed to evaluate the effect of low-dose radiation during childhood on long-term neurocognitive function.

INTRODUCTION

While some studies show that childhood exposure to high-dose radiation such as that administered in cranial radiation therapy (CRT) for leukemia and brain tumors leads to neuropsychological decline for up to about 35 years (*1–3*), other studies differ, including two Swedish studies on the effect of low-dose radiation used to treat children aged under 18 months of age for cutaneous hemangioma (*4*, *5*). Hall et al. showed a negative dose-response relationship for the cognitive tests of learning ability and logical reasoning in the 1930–1960 Stockholm cohort (*4*) while in the Stockholm and Gothenburg study, the 1950–1960 cohort showed no clinically relevant effect on global cognition in 18-year-olds (*5*).

In studies dealing with the cognitive effects of nontherapeutic radiation exposures, Sibley et al. showed that the maximum annual and total lifetime radiation doses were related to death from dementia in female nuclear weapons workers (*6*) while Yamada et al. reported that cognitive function among total-body-irradiated atomic bomb survivors after adolescence was not significantly associated with radiation dose (*7*).

Here we aimed to reveal the association between late-life neurocognitive function and radiation exposure among childhood atomic bomb survivors in the Adult Health Study (AHS) of the Radiation Effects Research Foundation (RERF). We used the Childhood Cancer Survivor Study Neurocognitive Questionnaire (NCQ), a subjective self-reported measure of neurocognitive function developed to investigate the neurocognitive effects of therapy for the Childhood Cancer Survivor Study (*8*).

MATERIALS AND METHODS

Since 1958, to investigate the health effects of exposure to ionizing radiation, the RERF Adult Health Study (AHS) has conducted biennial health check-ups of people who were in Hiroshima or Nagasaki at the time of the atomic bombings. The cohort was

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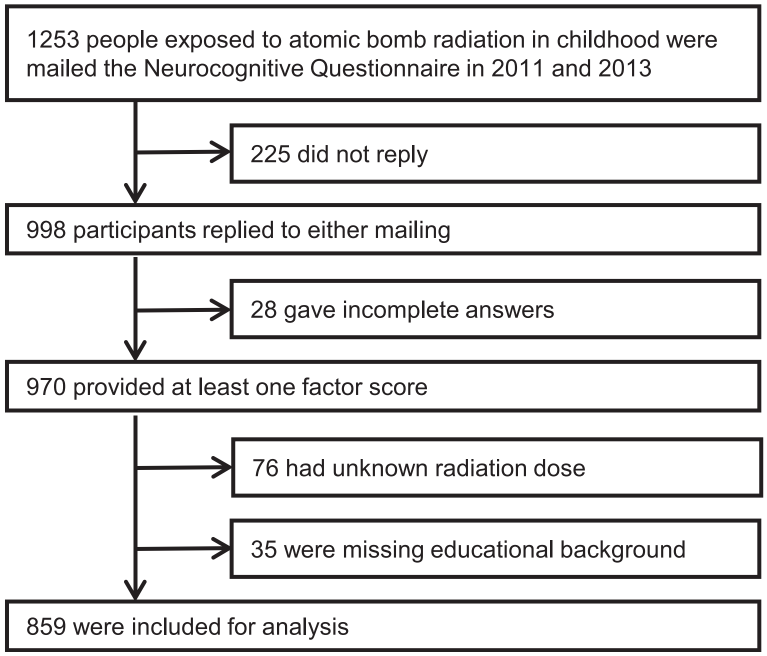

FIG. 1. Flowchart showing study participants

expanded in 1977 (*9*), and since 1995, the AHS has also conducted semiannual mail surveys to obtain additional health information for members of the cohort who had expressed willingness to participate in such a survey. In 2011 and 2013, to examine late-life neurocognitive functions, we mailed the NCQ to everyone who might be eligible for the mail survey with written instructions (*10*). The RERF Institutional Review Board approved the study. Among members of the mail survey, 1,253 subjects were exposed at 12 years of age or younger (Fig. 1). The NCQ is a self-administered screening tool including 25 subjective neurocognitive complaints over the past six months (*8*) with options of the following responses: 1 = ''Never a Problem'', 2 = ''Sometimes a Problem'', and 3 = ''Often a Problem''. Using exploratory factor analysis among the cohort control participants in a previous study (*10*), we identified 4 factors representing 20 of the 25 NCQ items. We labelled them metacognition (Factor 1, 9 items), emotional regulation (Factor 2, 5 items), motivation/organization (Factor 3, 4 items), and processing speed (Factor 4, 2 items) (*10*). Supplementary Table S1 (https://doi.org/10.1667/RADE- 21-00122.1.S1) shows items included in each factor. We calculated raw scores for each factor as the sum of items.

Figure 1 is a flowchart of the study participants; 508 were control subjects (brain dose estimated by DS02R1 (*11*) $<$ 5 mGy), 641 were exposed ($\geq$ 5 mGy), and 104 were unknown-dose subjects. The estimated median brain dose of the exposed was 515 mGy (interquartile range, 177–1,043). We used all subjects who provided at least one factor score for either test. Among mail subjects, that included 80.0 % of control subjects and 76.4% of exposed subjects.

In the analyses, we used both NCQ scores in two surveys for those who answered both questionnaires and applied random intercept models of linear and generalized linear mixed effects models for continuous and binary responses to express the within-participant correlation induced by the measurements obtained from the same individuals, respectively (see Supplementary Data Appendix, https://doi.org/10.1667/RADE- 21-00122.1.S1). In the analyses, we converted factor raw scores to T scores, whose mean (SD) of the control was 50 (10). Higher scores indicated more problems in neurocognitive function. We assumed that the participant was ''impaired'' for a corresponding group when a T score was in the upper 10th percentile of the control (i.e. T score $\geq$ 63). This cutoff definition was used in the standardization manual for the Brief Symptom Inventory-18 (*12*) and in the studies of the Childhood Cancer Survivor Study (*3, 13*).

We performed a separate analysis to estimate the effects of radiation exposures (which were treated as continuous values) to the T scores of each factor after adjusting demographic covariates. The demographic covariates included age at the test (the age was centered and divided by 10), sex, city, and education (primary school, high school, and university). We also estimated the odds ratio of prevalence of ''impaired'' in the above definition (percentage impaired) using the logistic models.

We estimated the parameters of random intercept models using Bayesian inference. We used OpenBUGS version 3.2.3 (http://www.openbugs.net); MCMC software for Bayesian inference and R version 3.5.3 for other statistical analyses.

RESULTS

The study included 859 participants (390 control and 469 exposed). Five-hundred-and-eighty participants (270 control and 310 exposed) provided at least one factor score for both NCQ. Their mean (SD) ages at the time of the bombing were 6.4 (3.8) years (6.7 (3.8) for the control, 6.1 (3.8) for the exposed, $p = 0.026$) and 73.7 (3.8) years (74.0 (3.8) for the control, 73.5 (3.8) for the exposed, $p = 0.035$) at the time of replying to the questionnaire.

Table 1 shows the sex, city of exposure, and education level of the participants. The control and the exposed did not differ significantly in sex or education level, but the exposed included significantly more Hiroshima survivors.

Table 2 shows the association of those features with radiation exposure, T score, and percentage impaired for each NCQ factor. We showed estimates for T score and odds ratios for percentage impaired with 95% Bayesian confidence intervals (CIs) in the models for 4 NCQ factors. Both T scores and percentage impaired for all factors tended

TABLE 1
Demographic Features of Control and Exposed Subjects

Feature, n (%)	Total N = 859	Control N = 390	Exposed N = 469	*P*
Male	342 (39.8%)	160 (41.0%)	182 (38.8%)	0.554
Hiroshima	525 (61.1%)	212 (54.4%)	313 (66.7%)	<0.001
Education level				0.836
Primary school	229 (26.7%)	102 (26.2%)	127 (27.1%)	
High school	485 (56.5%)	219 (56.2%)	266 (56.7%)	
University	145 (16.9%)	69 (17.7%)	76 (16.2%)	

to increase with age. We could not find a city difference in any endpoints. Females showed more deterioration in Factors 3 and 4 of T score and Factor 4 of percentage impaired. Higher education tended to be associated with lower T scores in Factors 1 and 4 and lower percentage impaired in Factors 1 and 2. We could not find a radiation effect associated with any T score of the four factors or with the percentage impaired except for Factor 3. For Factor 3, percentage impaired increased significantly with radiation dose [Odds ratio per 1 Gy: 2.77, 95% CI (1.35, 6.48)] without significant increase of mean T score.

DISCUSSION

We have shown here that subjective cognition in late life of participants who were exposed to radiation in childhood was associated with age and partially with sex and education. This result is similar to our previous report for non-exposed subjects, including those aged 66 to 89 years (*7*).

Few reports can be found on the association of demographic features with subjective cognition. Age is the most significant risk factor for dementia as shown by the Adult Changes in Thought (ACT) cohort study (*14*), the European Studies of Dementia (EURODEM) study (*15*), and the Framingham study (*16*). Lower education levels were associated with Alzheimer's disease, but not with non-Alzheimer's disease dementia in the ACT and EURODEM studies (*14, 15*), while the ACT study showed no association of sex with Alzheimer's disease (*14*). Significant deterioration of processing speed (Factor 4) in females in this study is compatible with the results of objective cognition on reaction time (a measure of processing speed) reported that males have faster and less variable reaction times than females (*17*).

In this study of adults exposed to atomic bomb radiation in childhood, we found no radiation effect in 4 factors of subjective cognition other than for the percentage impaired for motivation/organization. Although dose responses to CRT have been reported in children treated for central nervous system tumors (*18*), adults who as children received 24 Gy CRT, but not 18 Gy CRT, showed impairment in immediate or delayed memory (*19*). Children with cutaneous hemangioma after radiation therapy of brain doses up to 250 mGy had no clinically relevant effect on cognition (logical, spatial, technical, verbal or global test scores) at 18 years of age, but, only in the verbal test, with the highest dose group (>250 mGy, median 680 mGy) showing a decreasing score (*5*). In our study, the median estimated brain dose was 515 mGy, which appears to be below the dose causing cognitive decline.

TABLE 2
Association of Demographic Factors and Radiation Exposure with Estimates for T Score and Odds Ratios for Percentage Impaired for 4 NCQ Factors

	Male (vs. Female)	Age (/10 years)	Nagasaki (vs. Hiroshima)	Education (vs. primary school): High school	Education (vs. primary school): University	Exposure dose (/Gy)
T score (95% CI)						
Factor 1	–0.51	**3.31**	0.90	**–1.66**	**–2.42**	0.20
Metacognition	(–1.87, 0.89)	**(1.80, 4.86)**	(–0.52, 2.26)	**(–3.17, –0.08)**	**(–4.46, –0.21)**	(–0.78, 1.21)
Factor 2	–1.06	**2.09**	0.11	–0.96	–1.59	–0.26
Emotional regulation	(–2.40, 0.29)	**(0.56, 3.69)**	(–1.26, 1.45)	(–2.60, 0.62)	(–3.59, 0.47)	(–1.24, 0.71)
Factor 3	**–1.64**	**3.63**	–0.47	–0.66	–0.88	0.85
Motivation/Organization	**(–3.01, –0.28)**	**(2.05, 5.20)**	(–1.88, 0.87)	(–2.20, 0.86)	(–2.94, 1.17)	(–0.16, 1.81)
Factor 4	**–1.61**	**4.33**	–0.74	**–2.20**	**–2.13**	0.47
Processing speed	**(–2.88, –0.31)**	**(2.83, 5.83)**	(–2.03, 0.58)	**(–3.71, –0.71)**	**(–4.14, –0.18)**	(–0.51, 1.45)
Odds ratios for percentage impaired (95% CI)						
Factor 1	0.63	**12.17**	1.58	0.49	**0.16**	0.97
Metacognition	(0.19, 1.82)	**(3.34, 58.33)**	(0.54, 4.81)	(0.14, 1.58)	**(0.02, 0.82)**	(0.42, 2.23)
Factor 2	0.41	**4.02**	1.28	0.45	**0.22**	0.89
Emotional regulation	(0.14, 1.06)	**(1.32, 13.56)**	(0.49, 3.39)	(0.15, 1.25)	**(0.04, 0.96)**	(0.41, 1.78)
Factor 3	0.40	**17.29**	0.87	0.65	0.43	**2.77**
Motivation/Organization	(0.12, 1.14)	**(4.64, 90.83)**	(0.28, 2.55)	(0.18, 2.20)	(0.07, 2.23)	**(1.35, 6.48)**
Factor 4	**0.37**	**16.07**	0.75	**0.29**	0.32	1.14
Processing speed	**(0.14, 0.82)**	**(5.83, 53.52)**	(0.32, 1.72)	**(0.10, 0.71)**	(0.08, 1.10)	(0.60, 2.15)

Notes. Sample sizes were 820, 816, 838, and 844 for Factor 1, Factor 2, Factor 3, and Factor 4, respectively. Scores were adjusted by age at the test, sex, city, and education. Items with significant difference were expressed in bold font. NCQ: Neurocognitive Questionnaire

Some studies evaluated radiation effects using a subjective cognitive scale. A study after the Chornobyl accident showed the memory problems assessed by a self-reported questionnaire and university attendance of the infant evacuees did not differ from those of the control (*20*). In adult survivors who had received radiation for CNS tumors or leukemia at adolescent and early young adult, the NCQ score was high for those who had received CRT but not noncranial radiation therapy (*21*).

In non-CNS cancer survivors, radiation exposure was associated with impairment in task efficiency, memory, and emotional regulation among those diagnosed at less than 6 years of age (*13*). Young acute lymphoblastic lymphoma or low-grade glioma patients who received CRT showed abnormalities on brain parts related to cognition, such as global cortical atrophy, many white matter hyperintensities, low temporal lobe or hippocampal volume, and thin parietal and frontal cortices (*19, 22*), even among subjects exposed to a low-fractional dose ($\leq$2 Gy). Our study that included people exposed to atomic bombings at less than 13 years of age did not reveal a relationship between radiation and cognition (*7*), nor did our previous study on objective cognition for people exposed at or over 13 years of age (*7*).

The factors we selected from our baseline study (*7*) included 20 out of 25 NCQ items. The limitations of this study are that non-respondents (225, Fig. 1) might have had poorer cognitive function, and that 97% (970/998, Fig. 1) of the respondents addressed at least one factor, but not necessarily all the selected NCQ items. Completeness of each factor was related to sex, age, and education. However, we could not find the relationship between the completeness and radiation dose. Another limitation is that this study was evaluated by subjective complaints. Although such complaints are related to objective cognition (*23, 24*) or to a hippocampal volume decrease in the elderly (*23*), additional study on objective cognition is called for. Nevertheless, our survey was taken 67 years postirradiation, so our results may contribute to the long-term effects on cognition of low- to medium-radiation exposure in the young.

SUPPLEMENTARY DATA

Appendix: Mathematical information.

Supplementary Table S1: The List of NCQ Items for the Four Factors.

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