Association Between Dementia and Midlife Risk Factors: the Radiation Effects Research Foundation Adult Health Study

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OBJECTIVES: To investigate the association between midlife risk factors and the development of vascular dementia (VaD) or Alzheimer's disease (AD) 25 to 30 years later.

DESIGN: A prevalence study within a longitudinal cohort study.

SETTING: Subjects in the Adult Health Study (a prospective cohort study begun in 1958) have been followed through biennial medical examinations in Hiroshima, Japan.

PARTICIPANTS: One thousand seven hundred seventy-four subjects in Hiroshima, Japan born before September 1932 (1,660 with no dementia, 114 with dementia (51 with AD, and 38 with VaD) diagnosed from 1992 to 1997 according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria).

MEASUREMENTS: The subjects were examined for effect on dementia of sex, age, education, atomic bomb radiation dose, and midlife factors associated with risk (smoking, alcohol intake, physical activity, dietary habits, systolic blood pressure (SBP), body mass index, and history of diabetes mellitus) that had been evaluated in 1965–1970.

RESULTS: VaD prevalence increased significantly with age, higher SBP, and lower milk intake. The odds ratios of VaD for age (in 5-year increments), SBP (10 mmHg increments), and milk intake (almost daily/less than four times a week) were 1.29, 1.33, and 0.35, respectively. The risk factors for VaD were compatible with the risk factors for stroke in this study population. AD prevalence increased significantly with age and lower education. Other midlife factors and radiation dose did not show any significant association with VaD or AD.

CONCLUSION: Increased SBP and low milk intake in midlife were associated with VaD detected 25 to 30 years later. Early behavioral control of the risk factors for vascular disease might reduce the risk of dementia. **J Am Geriatr Soc 51:410–414, 2003.**

Key words: vascular dementia; Alzheimer's disease; midlife risk factors

The older population in Japan, North America, and Western countries is increasing, and the trend is predicted to continue. Because risk of dementia increases with age, the number of individuals with dementia is expected to increase as well.[1–3] Clarification of the long-term effect of risk factors is important, because some risk factors are modifiable for prevention of dementia.

Prevalence cases of dementia were identified based on the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised* (DSM-III-R) in the Adult Health Study (AHS) of the Radiation Effects Research Foundation (RERF) between 1992 and 1996 in the previous dementia prevalence study, which has been described elsewhere.[3] Multivariate logistic analysis conducted in that study to investigate the relationship between risk factors and vascular dementia (VaD) suggested a strong association between VaD and history of stroke. Although the association between stroke and VaD has been demonstrated in many other studies[2,4] and risk factors of stroke are well known, it is not clear which of the risk factors for stroke lead to VaD.

In the AHS, information regarding midlife risk factors of stroke, such as blood pressure, diabetes mellitus, smoking, alcohol intake, physical activity, and dietary habits was obtained from clinical examinations and questionnaires. Analysis using such midlife risk factors, which were not susceptible to systematic recall error, had the advantage of elucidating the association between dementia and the risk factors. A large-scale epidemiological cohort study (the Ni-Hon-San Study) conducted on Japanese men living in Japan (the AHS cohort) and in Honolulu (the Honolulu

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Heart Program)[5] in the 1970s, showed that the incidence of stroke was about three times as high in Japan as in Hawaii. Age and blood pressure were the most important risk factors for stroke, and intake of animal protein and saturated fat was inversely associated with stroke in both regions.[5]

Although some reports suggest that cerebrovascular disease plays an important role in Alzheimer's disease (AD),[4,6] the relationship between AD and stroke or vascular risk factors such as hypertension, diabetes mellitus, and smoking is controversial.[7–12] Regarding the relationship between dietary habits and AD, White et al. reported that in the Honolulu Asian Aging Study, higher tofu (soy bean curd) consumption was independently associated with brain atrophy.[13]

To examine the relationship between VaD and AD and midlife risk factors, data for 1,774 subjects who participated in a recent dementia prevalence study and underwent clinical and epidemiological examination about 25 to 30 years ago was reviewed.

METHODS

The Atomic Bomb Casualty Commission (predecessor of the RERF) founded the AHS in 1958 to investigate illnesses and changes in physiological and biochemical function resulting from exposure to atomic bomb radiation.[14] The original cohort of atomic bomb survivors and control subjects consisted of residents of Hiroshima and Nagasaki selected from the 1950 national census supplementary schedules and the Atomic Bomb Survivors Survey. Members of the AHS participated in biennial health examinations.

In health examinations between September 1992 and August 1997, 2,463 members of the AHS who provided informed consent (84.5% of the eligible AHS Hiroshima population born before September 1932) were screened for dementia using the Cognitive Ability Screening Instrument (CASI),[15] which consists of items identical or similar to those used in the Mini-Mental State Examination or Hasegawa's Dementia Scale, widely used in epidemiological studies in Japan. A second examination was conducted for participants with low CASI score and participants selected randomly from among those with a high CASI score. The second examination included a neurological examination, completion of the Informative Questionnaire on Cognitive Decline in the Elderly by the caregiver, Hachinski's Ischemic Score, and the Clinical Dementia Rating. Dementia and its subtypes were classified according to DSM-IV criteria. The methods of evaluating prevalence have been described elsewhere.[3] Standardization exercises of clinical diagnosis of dementia and its subtypes using DSM-III-R and DSM-IV were developed as a part of a cross-national dementia study in which investigators from Seattle, Honolulu, and Hiroshima participated.[16] After two such exercises, agreement on dementia and its subtypes of VaD and AD was reached.

Information about education (number of years and level attained) and potentially risk-related midlife factors such as smoking, alcohol intake, and dietary habits was obtained from questionnaires self-administered from 1965 to 1968. The categories for smoking were never, former, and current. The categories for alcohol intake were never and former/current. The categories of eating with salt or soy sauce were always, after tasting, and seldom. Consumption frequency of fish, meat, tofu, and milk were less than twice a week, two to four times a week, and almost daily. Information about physical activity was obtained from a questionnaire self-administered between 1968 and 1970. Physical activity index (PAI) was calculated from occupational and leisure activities.[17] Information about systolic blood pressure (SBP), body mass index (BMI), and diagnosis of diabetes mellitus was obtained from an AHS physical examination conducted between 1965 and 1968. Diagnosis of diabetes mellitus was based on glucose tolerance tests or a history of treatment for diabetes mellitus.

The logistic regression analysis was used for 1,774 of the 2,463 dementia prevalence study subjects who had provided all midlife risk factor information. The dependency of prevalence of VaD and AD on those risk factors (smoking, alcohol intake, physical activity, dietary habit, SBP, BMI, and diabetes mellitus) was examined. Sex, age at time of dementia screening test, education level, and atomic bomb radiation dose were also considered as variables. Individual radiation dose estimates were based on the RERF 1986 Dosimetry System (DS86).[18]

In statistical analysis, parameters were estimated using maximum likelihood methods, and significance of the parameter estimate was based on the likelihood ratio test. First, each risk factor was analyzed using univariate logistic regression with adjustment for age, sex, and education. Because smoking status showed a remarkable sex difference, the smoking effect was analyzed separately for men and women. Then multivariate logistic regression was examined, including variables found to be significantly associated with VaD or AD. After nonsignificant terms were removed from the model, the final model was obtained. Computations were performed using SAS software for logistic regression analysis (SAS Institute, Inc., Cary, NC).

RESULTS

Average age and education level did not differ significantly between the 1,774 study subjects and the 689 excluded subjects except that the education level was lower for male study subjects than for male excluded subjects ($P = .04$). Women constituted 73.2% of the study subjects. There was a greater proportion of women because many men were in military service outside of Japan at the time of the bombing, and women in Japan lived longer than men. The characteristics of the subjects at baseline are shown in Table 1. The younger age group had a higher educational level than the older age group. The mean BMI was higher for women than for men. Most people in the high SBP group in late life showed normal SBP in midlife (data not shown). The proportion of current smokers differed dramatically between the sexes.

Dementia was diagnosed for 114 (6.4%) of the 1,774 subjects. It included 38 cases of VaD and 51 cases of AD.

Univariate logistic regression analysis with adjustment for age, sex, and education level was performed. Table 2 shows all variables for which there is a relationship of $P <$ .15 for VaD or AD. Increased SBP and low milk intake were possible risk factors for VaD. For milk intake, almost daily consumption (frequency, 42%) was associated with a significantly lower likelihood of VaD. Increased SBP and a history of diabetes mellitus were possible risk factors for AD. Smoking, alcohol intake, PAI, BMI, other dietary

Table 1. Characteristics of Subjects at Baseline (N = 1,774)

Sex	Age in 1965	N	Education (years)	Body Mass Index (kg/m²)	Physical Activity Index	Systolic Blood Pressure (mm Hg)	Smoking Status (%)		
							Never	Former	Current
Male	30s	290	10.2	20.7	20.9	116	15.9	4.8	79.3
	40s	88	9.5	21.0	19.7	118	17.0	8.0	75.0
	50s	83	9.3	21.5	19.1	121	18.1	12.0	69.9
	60s	13	8.5	21.0	18.5	123	38.5	7.7	53.8
	70s	1	6.0	20.0	17.2	160	100.0	0.0	0.0
Female	30s	444	9.7	21.5	19.6	111	90.3	0.0	9.7
	40s	526	9.0	22.5	20.2	117	85.6	1.0	13.5
	50s	274	8.4	22.1	19.9	123	88.7	1.8	9.5
	60s	44	8.0	22.3	19.8	132	93.2	2.3	4.5
	70s	11	7.6	20.8	18.4	145	90.9	0.0	9.1

habits, and radiation dose did not show any significant effects on prevalence of VaD or AD.

Preliminary multivariate logistic regression was performed including age, sex, education level, and all variables that showed a significant association with VaD or AD in the univariate logistic regression. The result of the final model from which nonsignificant terms were removed is shown in Table 3. For VaD, prevalence increased significantly with increasing age and higher SBP in midlife. Higher intake of milk in midlife protected against VaD. Sex and education level did not affect VaD prevalence. The odds ratios (ORs) of VaD for age (in 5-year increments), SBP (10-mmHg increments), and milk intake (almost daily intake/less than four times a week) were 1.29, 1.33, and 0.35, respectively (overall chi-square (χ^2) = 45.8, $P < .0001$) The prevalence of AD increased significantly with increasing age and lower education. Sex, SBP, and history of diabetes mellitus did not show any significant effect in multivariate logistic regression. The ORs for AD for age (in 5-year increments) and education (in 3-year increments) were 2.48 and 0.41, respectively (overall χ^2 = 143.6, $P < .0001$). Although the number of VaD cases decreased to 35 and of AD to 36, 1,705 subjects who were younger than in 1965 were also examined using multivariate logistic regression. The results for those subjects (ORs of VaD for age, SBP, and high milk intake were 1.45, 1.38, and 0.31, respectively, and ORs of AD for age and education were 2.97 and 0.36, respectively) were similar to the results for the 1,774 subjects.

DISCUSSION

This analysis of the association between dementia and midlife risk factors had the advantage of being based on a protocol similar to the one used in the Honolulu Asian Aging Study, wherein data on midlife characteristics were collected before the onset of dementia and therefore did not suffer from systematic recall error.

The previous report on prevalence of dementia in the AHS cohort was based on 2,222 subjects screened between 1992 and 1996.[3] In the present report, the study period was 1 year longer, the subjects were limited to those who provided all information on midlife risk factors, and the diagnostic criteria were those of DSM-IV. Crude prevalence of all dementia and AD in the present study was slightly (0.5%) lower than in the previous report, whereas crude prevalence of VaD was slightly (0.3%) higher.

In the present study, elevated SBP in midlife was a significant risk factor for VaD prevalence about 30 years

Table 2. Univariate Logistic Regression with Adjustment for Age, Sex, and Education

Variable	Vascular Dementia		Alzheimer's Disease	
	Odds Ratio	*P*-value	Odds Ratio	*P*-value
Body mass index, kg/m² increments	1.074	.134	0.989	.809
Systolic blood pressure, 10 mmHg increments	1.039	<.001	1.025	<.001
Diabetes mellitus, yes/no	1.282	.058	4.377	.007
Eating with salt or soy sauce after tasting versus always eating with salt or soy sauce	0.654	.279	0.492	.062
Seldom eating with salt or soy sauce versus always eating with salt or soy sauce	1.061	.914	1.854	.110
Milk intake, 2–4 times a week versus less than twice a week	0.418	.107	0.741	.485
Milk intake, daily versus less than twice a week	0.257	.002	0.633	.145

Table 3. Multivariate Logistic Regression

Risk Factor	Odds Ratio (95% Confidence Interval)	*P*-value	Chi-Square
For vascular dementia			
Age, 5-year increments	1.29 (1.05–1.59)	.014	6.08
Systolic blood pressure, 10 mmHg increments	1.33 (1.14–1.56)	<.001	12.92
Milk intake, almost daily versus <4 times a week	0.35 (0.14–0.77)	.014	5.99
For Alzheimer's disease			
Age, 5-year increments	2.48 (2.00–3.12)	<.001	64.34
Education, 3-year increments	0.41 (0.25–0.67)	<.001	12.03

later, in spite of the fact that most people in the high SBP group in late life showed normal SBP in midlife. A history of stroke or hypertension before dementia screening was a significant risk factor for VaD in the previous AHS dementia study.[3] Similarly, a population-based incidence study of dementia in Hisayama, Japan, showed that SBP at baseline examination about 7 years before the study influenced the development of VaD independently of stroke.[2] The Ni-Hon-San study showed that age and blood pressure are the most important risk factors for stroke. Elevated SBP in midlife may contribute not only to VaD with stroke, but also to VaD without stroke through silent small-vessel disease and extensive white-matter changes, because some reports suggest that elevated blood pressure contributes to small-vessel disease and white-matter hyperintensities seen in neuroimaging.[19,20]

Lower intake of milk in midlife was predictive of VaD in the present study. This result is consistent with the Honolulu Asian Aging Study conclusion that unknown factors related to a Western diet may protect against developing VaD, with or without stroke,[21] because, in the dietary acculturation questionnaire used in the Ni-Hon-San study, tofu was considered an indicator of traditional Japanese food habits, fish and meat were considered common to both East and West, and milk intake was taken as an indicator of Westernization.[22] In the Ni-Hon-San Study, animal protein and saturated fat intake was inversely associated with stroke not only in Japanese men, but also in Japanese-American men.[5] Because animal protein and saturated fat intake was calculated for only a portion of men in the AHS, its association with VaD was not considered in this analysis. Although the risk of mortality from cerebrovascular disease in other Japanese populations is inversely associated with milk consumption,[23] the relationship between milk intake and VaD may be a proxy for Westernization of dietary habits, rich animal protein and saturated fat intake, or other socioeconomic factors. A more detailed investigation is required to elucidate whether dietary habits protect against VaD by reducing stroke or other mechanisms.

The effect of SBP and diabetes mellitus on AD in univariate logistic regression with adjustment for age, sex, and education was lost in multivariate logistic regression. Mean baseline SBP at age 40 in this study was 118 mmHg for men and 117 mmHg for women. Swan et al. suggest that midlife SBP (mean SBP at age 47 = 128 mmHg) is a significant predictor of decline in cognitive function and magnetic resonance imaging (MRI) volumetric measures of brain atrophy in late life (mean age = 72) in the prospective U.S. National Heart, Lung, and Blood Institute Twin Study.[24] In a longitudinal study of blood pressure and dementia, Skoog et al. showed that hypertension increases the risk of AD.[7] Because baseline SBP in the current study population was lower than in others,[7,24] it might be difficult to detect its effect on developing AD in late life. Vascular risk factors and atherosclerosis are associated with microvascular lesions such as white-matter lesions.[25] If AD cases diagnosed using DSM-III/R or DSM-IV criteria included some microvascular dementia without clinical stroke events, such as Binswanger's type dementia, and because microvascular dementia often shows insidious onset and slow progression, the relationship between AD and vascular risk factors may be emphasized by such contamination. In this study, computed tomography scans or MRI for about 25% of dementia cases were reviewed. Based on neuroimaging review, cases that exhibited insidious onset and slow progression with white-matter lesions or silent cerebral infarction were excluded from the category of AD. Cases with unconfirmed deteriorating courses were not included in AD. Differences in diagnostic criteria of AD used and percentage of neuroimaging examination employed may have led to conflicting results regarding the relationship between AD and vascular risk factors.[7–11]

In the Honolulu Asian Aging Study, higher tofu consumption in midlife was independently associated with late-life indicators of cognitive impairment and brain atrophy,[18] but in the current study, tofu intake did not affect VaD or AD. Because tofu is eaten more frequently in Japan than in Hawaii, other factors might confound the effect of midlife tofu consumption on AD in Hawaii.

In conclusion, this investigation into the association between midlife risk factors and the development of dementia took advantage of RERF's extensive longitudinal database on health status and habits and a recent assessment of dementia in the AHS population. VaD prevalence increased significantly with age, higher SBP, and lower intake of milk. AD prevalence increased significantly with age and lower education. Although participants in the present analysis do not represent the general Japanese population, because they are primarily atomic bomb survivors and their controls, the radiation dose for one-third of

participants was 0. Because radiation exposure did not show any significant effect on dementia prevalence, and because other disease morbidities in the AHS are compatible with other published Japanese estimates,[14] the result of this analysis can be extrapolated to the general population. Early behavioral control might reduce dementia risk.

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