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Reduced contribution of hypertension to the risk of silent brain infarction in the elderly: a population-based study in Takahata, Japan

Michio Sagae, Toru Kawanami, Hikaru Nagasawa, Shingo Koyama, Hideki Kimura, Shigeki Arawaka, Manabu Wada, Keiji Kurita, Makoto Daimon, Takeo Kato

The Third Department of Internal Medicine, Yamagata University School of Medicine

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ABSTRACT

The prevalence of asymptomatic ischemic brain lesions among the healthy elderly is high. We present a population-based cross sectional study of 240 subjects aged 70 years old (the Takahata Study), in which we have investigated the contributions of hypertension and other cerebrovascular risk factors to silent brain infarctions (SBI) in the elderly people. Of the 240 study subjects, 217 (90.4%) had SBIs. Hypertension was not significantly associated with SBIs. Further, diabetes mellitus, hypercholesterolemia, habitual drinking or smoking were also not associated with SBIs. We concluded that aging may weaken the association of hypertension and other risk factors with asymptomatic ischemic brain lesions.

Key words : risk factor, asymptomatic cerebrovascular disease, elderly people, hypertension

INTRODUCTION

Brain magnetic resonance imaging (MRI) frequently detects ischemic lesions in the healthy elderly people with no stroke episodes [1), 2)]. The National Institute of Neurological Disorders and Stroke (NINDS) has proposed the term "asymptomatic cerebrovascular disease" to describe patients who present with no neurological symptoms or dementia but have abnormal findings on brain CT or MRI examinations [3)]. Subsequent studies have revealed that asymptomatic cerebrovascular disease is clinically important in that it is a high risk marker for future symptomatic stroke [4), 5)] and cognitive dysfunction [6)]. Silent brain infarction (SBI), silent ischemic lesion and asymptomatic brain infarction are the synonyms for asymptomatic cerebrovascular

Address for Correspondence : Toru Kawanami, 2-2-2 Iida-Nishi, Yamagata, 990-9585, Japan

disease[1]. Here we have used SBI to describe the condition in which patients have no neurological and congnitive dysfunction but show brain ischemic lesions on MRI. Previous studies have suggested a number of risk factors for SBI, which are similar to those of symptomatic stroke[5), 7)]. Accordingly, hypertension and aging are considered to be strong risk factors for both SBI and symptomatic stroke[1]. However, while risk factors for symptomatic stroke have been studied extensively, those for SBI remain imcompletely understood[1].

Advances in the study of stroke have shown that some of the risk factors for symptomatic stroke diminish or lose their impact with advancing age. A recent meta-analysis of large epidemiological studies has suggested that the association of hypertension with symptomatic stroke appears to be weaker in the elderly[7]. Based on this finding, it is assumed that hypertension may have either a weak or no relationship with SBI in the elderly; however, no investigation has been performed to evaluate this assumption. The current study, a population-based cross sectional study, aimed to examine whether hypertension is associated with SBI in the elderly people.

SUBJECTS AND METHODS

Subjects

The subjects of the study included 269 healthy individuals who were 70 years old at the time of examination. The subjects were recruited from a healthcare examination conducted in the town of Takahata, Yamagata, a rural area in the northern part of Japan (Fig.1). The official population statistics showed that there were 350 individuals aged 70 years in the town,: 269 (76.9%) of them participated in this study. The remaining 81 individuals did not participate, because they were under medication in hospitals, were wheel-chair dependent, or had other reasons for non-participation. All the subjects who participated in the study provided written informed consent, and the Medical Committee of Yamagata University School of Medicine approved the study.

METHODS

The characterisitics of the subjects were assessed using standardized questionnaires, physical and neurological examinations, electrocardiography and laboratory examinations. The questionnaire included items related to the medical history, present medications, and smoking and drinking habits. Physical and neurological examinations were performed by qualified neurologists, and cognitive function was evaluated using a mini-mental state examination and revised edition of Hasegawa dementia scale. Subjects with a medical history of symptomatic stroke or transient ischemic attack, and those with neurological abnormalities, were excluded from the study, because of the possibility of symptomatic stroke. Laboratory examinations included complete blood cell counts, liver and renal function tests, and measurement of hemoglobin A1c (HbA1c), uric acid, total cholesterol, and HDL cholesterol levels.

DEFINITION OF RISK FACTORS

The risk factors were defined as described in the Funagata Study[8]: a population-based study with a study design identical to the present study design. Hypertension was defined to be present if the subject had a

Fig. 1. Location of Takahata, Japan

systolic blood pressure of ≧160 mmHg or a diastolic blood pressure of ≧ 95 mmHg. Subjects with a medical history of hypertension or those receiving prescribed antihypertensive medications were also defined as having hypertension. Diabetes mellitus was defined to be present if the value of HbA1c was ≧6.5% (normal range ≦6.4%). Subjects with a medical history of diabetes or those receiving prescribed anti-diabetic drugs or being treated with insulin injections were also considered to have diabetes. Subjects with a serum cholesterol concentration ≧220 mg/dl were said to have hypercholesterolemia. The presence of hyperurticemia was defined as a serum uric acid concentration of ≧8.0 mg/dl. Those with a medical history of hypercholesterolemia and hyperurticemia or those under medications for the hypercholesterolemia and hyperurticemia were said to have hypercholesterolemia and hyperuricemia, respectively. The presence of atrial fibrillation or ischemic heart disease was determined by routine 12-lead electrocardiography.

Table 1. Scores of the Ischemia Rating Scale

Score	Cerebral white matter	Basal ganglia, thalamus, brainstem, and cerebellum
0	No lesion	No lesion
1	One or more lesion of <5 mm in size and/or 1-5 lesions of 5-9 mm in size	One or more lesion of <5 mm in size
2	≧6 lesions of 5-9 mm in size and/or One or more lesion of ≧10 mm in size	One or more lesion of 5-9 mm in size
3	Diffuse lesion	One or more lesion of ≧10 mm in size

BRAIN MRI STUDY

Brain MRI study was performed using a 0.3 T system (Elias; Hitachi-Medico, Japan). Transverse images were obtained as 7-mm thick sections. T1-weighted images (TR 500ms, TE 20 ms), T2-weighted images (TR 3500 ms, TE 112 ms) and fluid-attenuated inversion recovery (FLAIR) images (TR 6700 ms, TE 117 ms) were obtained. All the brain MRI images were evaluated by a qualified neuroradiologists who did not have any prior clinical information about the subjects. A high-intensity lesion on both T2-weighted and FLAIR images was considered to indicate an ischemic lesion. A high intensity lesion on T2-weighted images and a low intensity on T1-weighted images was considered to be an old cystic infarct, and was thus included as an SBI[9]. A small round spot (3 mm in diameter) that had a signal intensity identical to that of cerebrospinal fluid on T2-weighted and FLAIR images was considered to be an enlarged perivascular space[10], and thus excluded from the SBI lesions. Ischemic lesions were scored according to their number and size (Table 1).

STATISTICAL ANALYSIS

Using ischemic rating score (Table 1), incidence of ischemic brain lesions was expressed as the mean ± standard error (SE). Subjects were divided into 2 groups; those with hypertension and without hypertension. Mann-Whitney U-test was used to analyze the statistical difference between the 2 groups. Further, subjects were divided into 2 groups (Table 3): those with SBIs and those without SBIs. The data are expressed as the mean ± standard error (SE) and Mann-Whitney U-test was used to analyze the statistical significance of the differences in the variants between the 2 groups. Each candidate risk factors for SBI was evaluated by a multiple regression analysis or a multiple logistic regression analysis. In the multiple logistic regression analysis, a total ischemic score of ≧1 was defined as the presence of an ischemic brain lesion and a score of zero reflected the absence of a lesion. Statistical analyses were carried out using SPSS software. Statistical significance was set at a two tailed p value < 0.05.

Table 2. Incidence of brain ischemic lesions

	with hypertension n=151	without hypertension n=89
Brain lesion	139(92%)	78(88%)
Score		
Subcortical white matter	0.8±0.04	0.7±0.1
Deep white matter	1.3±0.1	1.2±0.1
Basal ganglia	1.0±0.1	0.7±0.1
Thalamus	0.3±0.04*	0.1±0.03*
Brainstem	0.2±0.04	0.1±0.04
Cerebellum	0.1±0.03	0.1±0.04
Total scores	3.6±0.2*	2.8±0.2*

Data are mean±SE. *p<0.05 by Mann-Whitney U-test.

Table 3. Characteristics of subjects with and without asymptomatic ischemic lesions

	With Ischemic Lesion n=217	Without Ischemic Lesion n=23	
Sex(Men/Women)	77/140	9/14	n.s.
Hypertension	139 (64.1%)	12 (52.2%)	n.s.
Diabetes Mellitus	31 (14.3%)	2 (8.7%)	n.s.
Hypercholesterolemia	80 (36.9%)	7 (30.4%)	n.s.
Hyperuricemia	21 (9.7%)	0 (0.0%)	n.s.
Atrial fibrillation	5 (2.3%)	0 (0.0%)	n.s.
Excessive drinking	14 (6.5%)	2 (8.7%)	n.s.
Smoking	70 (32.3%)	9 (39.1%)	n.s.

n.s. : not significant

RESULTS

Of the initial 269 subjects, 24 were excluded from the study because of a medical history of transient ischemic attack (TIA) or symptomatic stroke (14 individuals), and the presence of cognitive dysfunction (10 individuals). Five individuals were excluded because they had not been examined by neurologists. Finally, a total of 240 subjects (86 men and 154 women) were included in the study (Fig.2).

The incidence of the brain ischemic lesions was estimated with the ischemia rating scale and the total score on the scale was correlated with the presence of hypertension (Table 2). The scores of the various brain regions showed no significant difference except for the thalamus, which had an increased score in the subjects with hypertension.

The characteristics of the 240 subjects are summarized in Table 3. Of the study subjects, 217 (90.4%) had one or more ischemic lesions, and 23 subjects (9.6%) had no ischemic lesions. There were no statistically significant differences between the characteristics of the 2 groups. Laboratory examinations showed that serum concentrations of cholesterol, uric acid

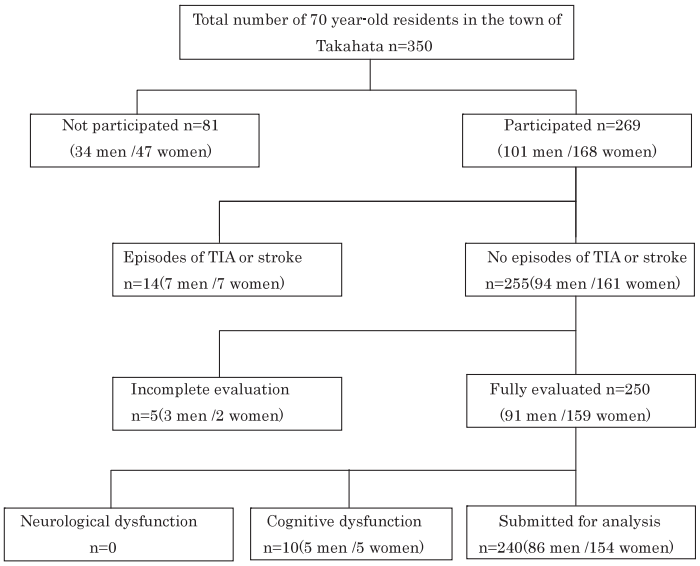

Fig. 2. Flow chart of the study population

Table 4. Risk factors for ischemic lesion by multiple logistic regression analysis

	Odds ratio	95%CI	p
Sex (Female/Male)	0.64	0.14－2.93	0.56
Hypertension	1.39	0.57－3.40	0.48
Diabetes Mellitus	1.99	0.43－9.28	0.38
Hypercholesterolemia	1.29	0.48－3.46	0.61
Excessive drinking	0.70	0.13－3.92	0.69
Smoking	0.74	0.16－3.37	0.70

CI : confidence interval.

and creatinine did not differ significantly between the 2 groups. The frequency of associated conditions, such as diabetes, was similar between the 2 groups. Data from the questionnaire showed that there had hardly been any movement of the population in Takahata town, particularly among the elderly aged around 70 years. Hence, most of the subjects had spent their life in the same natural environment and had followed the ethnic lifestyle of the area.

Table 4 shows the results of multiple logistic regression analysis for the candidate risk factors of SBI. The odds ratio for hypertension was 1.39 (95% confidence interval: 0.57-3.40, p=0.48), indicating that hypertension was not significantly associated with SBI. None of the other factors was found not to be a significant independent risk factors for SBI.

DISCUSSION

Hypertension has been considered to be a strong risk factor for SBI and symptomatic

stroke[1]. In accordance with the previous study[1], the total score and the score for the thalamus on the ischemic rating scale was significantly increased in the hypertensive subjects (Table 2). However, the comparison between the subjects with SBI and those without SBI showed that hypertension is not significantly associated with SBI (Table 3). A possible explanation for the discrepancy is that the different estimation methods of the brain ischemic lesions could result in the differences in the power of the statistical tests. Using the ischemia rating score (Table 1), the significant association between hypertension and SBI was demonstrated, possibly because not only the presence or absence of SBI but also severity of number and size of the ischemic lesions were included in the scoring. On the other hand, the comparison between subjects with SBI and those without SBI, the power of the statistical tests could be weak, resulting in failure to detect the significant association between SBI and hypertension (Table 3).

Another implication of the present study can be noted by a comparison of the present study with the Funagata study[8], which was also performed as a population-based cross sectional study that investigated the association between hypertension or other risk factors and SBI. Although their study design was essentially the same as that used in our study, the study subjects in the Funagata study were younger (mean age of the subjects in the Funagata study, 60 years). The odds ratio (OR) of hypertension for SBI was 3.06 (95% CI, 1.33-7.14) and 1.39 (95% CI, 0.57-3.40) in the Funagata study and the present study, respectively. Because the other risk factors did not differ between the two studies, we speculate that the contribution of hypertension to SBI may be lower among the eldery. In the Second Manifestations of ARTrial disease study[11], 308 subjects with a mean age of 58 years old were examined, and the OR for hypertension was found to be 2.2 (95% CI, 1.2-4.2). On the other hand, in the Rotterdam Scan Study[2], 513 subjects with a mean age of 71 years old were examined, and the OR for hypertension was 1.2 (95% CI, 0.6-2.4).

A similar age-related phenomenon has been observed in cerebrovasucular diseases including ischemic stroke. Based on the Hisayama study[12], Arima et al. found no association between hypertension and cardiovascular disease in elderly Japanese subjects aged 80 years and older. A further example is provided by the Framingham study[13], which showed a gradual decrease in the relative risk (RR) of hypertension for stroke with advancing age; the estimated RR was 3.5 in subjects aged 50-59 years old, but only 1.7 in subjects aged 80-89 years.

The present study has several limitations. The primary limitation is that the definition of hypertension was dependent on blood pressure measurements recorded on a single day. Although such measurements are reported to be acceptable in epidemiological studies[14], hypertension could have been underdiagnosed in the present study. However, in comparison with the Funagata study[8], which used a study design identical to that of the present study, we demonstrated weakening of the association between hypertension and SBI with advancing age. A second limitation is the number of the subjects without hypertension (n=23) was small, as compared with that of hypertensive subjects (n=217) (Table 3). This may reduce the statistical power, which may fail to detect the difference between the two groups. A third

limitation of our study is that some risk factors were not entirely evaluated. Hence, the contribution of atrial fibrillation and hyperuricemia to SBIs could not be estimated because of the small number of cases.

In conclusion, we have found that hypertensive risks for the elderly appear to be different from those for the middle-aged population. Therefore, to establish the evidence-based medicine for the elderly, clinical evidence should be obtained from the elderly, but not from the middle-aged people.

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