Abstract

Background

To investigate factors related to maximal intima-media thickness (max-IMT) of the carotid artery, particularly, plaques >1.5 mm, in a geographically coherent population in Japan.

Methods

Overall, 1,073 residents underwent carotid artery ultrasonography during the health screening conducted in Tochigi Prefecture, Japan, from October 2015 to March 2019. The observable visual field of max-IMT was evaluated in 929 cases without stroke or coronary artery disease. The results of a self-administered questionnaire survey examining vascular disease risk factors were assessed, and factors relating to max-IMT >1.5 mm were analyzed.

Results

Overall, 15.1% of the participants had max-IMT >1.5 mm. There were more elderly men and more hypertension (47.9% vs. 30.8%) in the max-IMT >1.5 mm group than in the max-IMT ≤1.5 mm group. The max-IMT >1.5 mm group had a higher prevalence of dyslipidemia and diabetes mellitus than the max-IMT ≤1.5 mm group. On logistic regression analysis, after adjusting for age and sex, hypertension (odds ratio, 1.54; 95%

confidence interval, 1.05-2.26; p=0.0284) was the sole predictor of max-IMT >1.5 mm.

Conclusion

Among residents in relatively high stroke mortality region, hypertension was related to max-IMT >1.5mm. For stroke prevention, we should employ screening tests for arteriosclerosis including carotid artery ultrasonography for patients with hypertension.

Keywords: Hypertension, Intima-media thickness, Carotid artery plaque, Carotid ultrasonography, Stroke

Introduction

Malignant neoplasia is the most common cause of death in Japan, followed by heart disease, senility, and stroke. The mortality rate of malignant neoplasia is 300.7 persons per 100,000, compared with 167.6 for heart disease and 87.1 for stroke. The combined mortality rate for heart disease and stroke is similar to that of malignant neoplasia [1]. Stroke is the second most common causal factor necessitating nursing care, and accounts for over 30% of bedridden cases. Therefore, the prevention of stroke is very important.

In Tochigi Prefecture, the mortality rate per 100,000 persons because of malignant neoplasms is well below the national average of Japan, although the average incidence of heart disease is almost 184.9 people/100,000 [2]. However, the stroke mortality rate is 110.3/100,000 persons, which is well above the national average of 100.5/100,000, which is the 14th lowest rate among the 47 Japanese prefectures [1].

Measurement of the carotid artery intima-media thickness (IMT) by ultrasonography is noninvasive and easy; it is widely used as a predictive marker for stroke and myocardial infarction because of its known association with cardiovascular disease and stroke onset [3-7]. A plaque is characterized when the max-IMT exceeds 1.5 mm, with a visible protrusion exceeding 0.5 mm, and when the protrusion is greater than 50% of the surrounding IMT [8]. Plaques exceeding 1.5 mm require detailed assessments of their characteristics [9].

IMT research involving the residents of Tochigi Prefecture, who have high age-adjusted stroke mortality rates, demonstrated that the max-IMT of the common carotid artery (CCA) is associated with hypertension and smoking [10]. However, that study failed to investigate plaques greater than 1.5 mm.

The current investigation assessed max-IMT values of the carotid artery, including the carotid bulbs (CB), together with factors linked to plaques measuring greater than 1.5 mm.

Materials and methods

The survey was conducted among 1,073 individuals who underwent carotid artery ultrasonography during a health screening assessment between October 2015 and March 2019. Almost all participants are general citizens living in Tochigi prefecture. Examinations were conducted at public hall or citizen center.

A self-administered questionnaire was completed prior to carotid artery ultrasonography, assessing age, sex, and vascular disease risk factors **(Table 1)**.

Carotid artery ultrasonography was performed by AI, RO, HT, AS, YT, and MO in a sitting position. One of the following ultrasonic diagnostic machines was used: LOGIQ e

Expert, LOGIQ e Premium (GE Healthcare Japan, Co., Ltd., Tokyo, Japan), CX 50 (Philips, Co., Ltd., Tokyo, Japan), ACUSON Freestyle (SIEMENS Japan, Co., Ltd.,Tokyo, Japan), Noblus (Hitachi, Co., Ltd., Tokyo, Japan), Aplio 300, Viamo, Xario 100, and Xario 200 (Toshiba Medical Systems, Co., Ltd., Tochigi, Japan).

IMT of the CCA and CB was evaluated long axis cross-section, using a linear-array probe (7.5 MHz or higher), with B-mode imaging, color Doppler imaging, and power Doppler imaging.

A total of 929 cases was analyzed with consent; 69 cases were excluded due to incomplete questionnaires and 75 due to the presence of known concomitant stroke or coronary artery disease. There were no cases of suspected Takayasu's arteritis, or circumferential IMT thickening.

Statistical analysis was conducted using IBM SPSS® for Mac, version 27 (Tokyo, Japan), in addition to a Mann–Whitney U test, Pearson's chi-square test, and logistic regression.

Inter-rater errors and max-IMT inter-rater errors were evaluated using intra-class correlation coefficients (ICCs) of five patient cases admitted to our University Hospital. All p-values were two-tailed, and values < 0.05 were considered significant.

Results

Data reliability tests

Both intra-rater and inter-rater reliability were satisfactory (ICC=0.85 and 0.83, respectively).

Background characteristics

Table 2 lists the demographic status of the study participants. To summarize, the median age was 66.0 years (20–89 years) and 29.7% (n = 276) were men. One hundred and four participants (11.2%) were smokers and 169 (18.2%) consumed alcohol daily. Hypertension was present in 33.4% of the participants (n=310); dyslipidemia, in 45.9% (n=426); and diabetes mellitus, in 12.7% (n=118). The median max-IMT value was 1.0 mm (range**,** 0.4–5.0).

Of the 929 cases, 140 (15.1%) exhibited max-IMT > 1.5 mm. Nine cases (1%) had CCA max-IMT and CB max-IMT > 1.5mm, and 140 cases (15.1%) had CB max IMT > 1.5 mm.

Factors associated with max-IMT > 1.5 mm

Participants were classified into two groups: max-IMT > 1.5 mm and ≤ 1.5 mm.

The median age of the max-IMT > 1.5 mm group was 71.5 years compared with 65 years in the ≤ 1.5 mm group. In the max-IMT > 1.5 mm group, 38.6% were men, compared with 28.1% in the ≤ 1.5 mm group. Hypertension was more common in the max-IMT > 1.5 mm group, at 47.9%, than in the max-IMT ≤ 1.5 mm group, at 30.8%. Dyslipidemia and diabetes mellitus were more likely to be found in the max-IMT > 1.5 mm group, but these differences did not achieve statistical significance and there was no difference in other factors (**Table 2**).

A logistic regression analysis was performed, analyzing dyslipidemia, diabetes mellitus, and hypertension, which were found to have a significant difference or trends in a univariate analysis. Results indicated that hypertension (odds ratio 2.06, p<0.0001) and diabetes mellitus (odds ratio 1.63, p<0.05) were associated with max-IMT > 1.5 mm in the univariate analysis. However, the result for dyslipidemia alone was not significant (p=0.0720) (**Table 3, Model 1**). The age-adjusted results indicated a relationship with hypertension (odds ratio 1.61, p = 0.0139) (**Table 3, Model 2**). However, although an association was suggested, diabetes mellitus (odds ratio 1.61, p = 0.0630) was not identified as a significant factor, whereas dyslipidemia showed no association. Results of the adjustment for sex (**Table 3, Model 3**) indicated that hypertension (odds ratio 2.04, p<0.001) was a significant factor, and was associated with diabetes mellitus (p=0.0649) and dyslipidemia ($p=0.0503$). In contrast, the age and gender adjustment results indicated that hypertension (odds ratio 1.54, $p<0.05$) was the only significant item. Although diabetes mellitus tended to show an association with IMT thickness ($p=0.0713$), dyslipidemia showed no such association ($p=0.151$) (**Table 3, Model 4**).

Discussion

In this study, we assessed the factors related to a max-IMT >1.5 mm, such as plaque characteristics, in a Japanese prefectural population who underwent carotid artery ultrasonography; i.e. individuals with relatively high levels of health consciousness. We investigated possible associations of IMT thickness >1.5 mm with hypertension and diabetes mellitus, both of which have been previously reported, particularly in the case of hypertension.

As represented by the Framingham study, hypertension is widely known to promote atherosclerosis [11], and a 4.4-year follow-up study of 11,547 hypertension patients reported that increases in IMT and mean blood pressure correlate with the onset of the first stroke [12]. Another report of 1,781 cases [13] indicated that age, systolic blood pressure, and fasting blood glucose were independent factors linked to IMT. It has also been reported that hypertension from childhood is strongly linked to IMT [14].

On the surface of vascular endothelial cells damaged by hypertension, the numbers of adhesion molecules such as VCAM-1 (vascular cell adhesion molecule-1), and chemokines such as MCP-1 (monocyte chemoattractant protein-1) are increased. These are produced to increase vascular permeability and allow monocytes and low-density lipoproteins (LDLs) to migrate under the intima. LDL forms foam cells with LDL oxide, thus contributing to plaque growth. The production of free oxygen radicals following the activation of NADPH oxidase via angiotensin II receptor stimulation, and the deterioration of endothelial cell function due to hypertension from blood vessel aging and mechanical stress, are also thought to promote atherosclerosis [15,16]. In addition, in our study, CB plaques were more frequent than CCA plaques in the max-IMT > 1.5 mm group, in which concomitant hypertension was more frequent than in the max-IMT ≤ 1.5 mm group. This point may suggest variation of wall share stress at bifurcation of internal carotid artery (ICA) and external carotid artery (ECA) cause CB plaque thickening. In previous studies, carotid bifurcation had a high risk of arteriosclerosis due to specific hemodynamics[17], and decreased wall shear stress promoted arteriosclerosis, resulting from decreased expression of VCAM-1 and reduced binding strength of endothelial cells[18,19]. These reports indicate that changes in wall share stress at carotid bifurcation may promote plaque formation in the CB.

The multivariate analysis results of a previous study [20] indicated a correlation between age, systolic blood pressure, and smoking with IMT in both men and women. Fasting blood glucose levels, high-density lipoprotein-cholesterol levels in men, and total cholesterol levels in women were also associated with IMT. Thus, in addition to hypertension, vascular disease risk factors such as smoking, diabetes mellitus, and dyslipidemia are also considered to contribute to IMT.

Smoking induces the production of reactive oxygen species, causing vascular endothelial cell disorders, vascular smooth muscle proliferation, and inflammatory cell invasion. It is associated with an increase in IMT and plaque formation [9,21]. In fact, in other previous reports, smoking was found to be related to CCA thickening [10]. That report indicated that 15% of participants were smokers, as opposed to 10% in the current study. This may be why no association with max-IMT > 1.5 mm was found.

Diabetes mellitus and dyslipidemia are known to increase IMT and are risk factors for cardiovascular events [22]. An association between very low-density lipoprotein-cholesterol levels and IMT has been reported in postmenopausal women [23]. It has also been shown that oral administration of statins for dyslipidemia may reduce IMT [24-26]. The current study found the associations between diabetes mellitus, dyslipidemia and max-IMT > 1.5 mm were not statistically significant, although diabetes mellitus was nearly so.

In the current study, men comprised 38.6% of the max-IMT > 1.5 mm group. Although enlargement of the intravascular space is related to an increase in IMT [27], the CCA diameter is known to be larger in men than in women [28]. We did not evaluate CCA diameters but this could explain the preponderance of men in the max-IMT > 1.5 mm group. A correlation between alcohol consumption and IMT thickness has previously been indicated [29,30]. Furthermore, association between alcohol consumption and plaque formation has also been suggested in smokers [31]. In our study, daily drinking was not associated with a max-IMT > 1.5 mm. However, if accurate daily alcohol intake could be evaluated, daily alcohol consumption might have been a significant factor of max-IMT>1.5mm.

It has been reported that snoring may cause arteriosclerosis. In particular, snoring is strongly associated with arterial effects in women, and it is known that prolonged snoring at night is linked to an increase in CCA [32]. Sleep apnea, especially obstructive sleep apnea, induces a cascade of events such as increasing sympathetic tone and renin-angiotensin-aldosterone system activation, due to hypoxemia and hypercapnia. This is postulated to result in the development of endothelial dysfunction, vasoconstriction, myocardial and vascular remodeling, and hypertension. Increased oxidative stress, release of inflammatory substances, enhanced lipolysis and insulin resistance ensue, resulting in left and right ventricular hypertrophy, left atrial dilation, carotid atherosclerosis, arterial stiffness, microvascular retinal changes, and microalbuminuria [33]. However, CCA IMT has been reported to differ according to the severity of sleep apnea, or the apnea hypopnea index (AHI) [34]. Since the current study did not assess snoring duration or AHI, it is possible that snoring and sleep apnea were not factors linked to max-IMT > 1.5 mm.

This study is limited in that it was based on a self-administered questionnaire; in addition, blood pressure, lipids, blood glucose control, the status of orally administered medications, and treatment period were unclear. This may have influenced our results, particularly with respect to the effects of daily drinking, dyslipidemia, diabetes mellitus, snoring, and sleep apnea. The difference of IMT between the treated and untreated groups is also unknown. Furthermore, IMT thickening due to atherosclerosis may not have been accurately excluded.

In addition, a selection bias occurred since participants were from a health-conscious population, who requested carotid artery ultrasonography at health screening.

Third, because we performed carotid ultrasonography by the long axis image of the sitting position, it was difficult to make precise CB evaluation of high-level branching cases. Furthermore, we did not assess the form and surface properties of plaques, nevertheless vulnerable atherosclerotic plaques such as echolucent plaque or jellyfish plaque are needed to analyze for prevention of stroke.

Conclusion

In a population with relatively high stroke mortality, screening carotid artery ultrasonography should be employed to help prevent strokes, as individuals with hypertension may have a max-IMT greater than 1.5 mm.

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