Incidence of Ischemic Stroke in Relation to Asymptomatic Carotid Artery Atherosclerosis in Subjects with Normal Blood Pressure. A Prospective Cohort Study.

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Incidence of ischemic stroke in relation to asymptomatic carotid artery atherosclerosis in subjects with normal blood pressure

A prospective cohort study

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Short title

Ischemic stroke and carotid artery atherosclerosis in normotensives

Key words:

Ischemic stroke, carotid IMT, carotid plaque, normotensive subject.

Abstract

Background

Approximately 10-20% of stroke cases have normal blood pressure (BP). The objective of this study is to explore whether the risk of ischemic stroke is related to the carotid intima-media-thickness (CIMT) and atherosclerotic lesions in a cohort of subjects with normal BP.

Methods

Common CIMT and presence of carotid plaque were determined by B-mode ultrasound in 6103 subjects, randomly recruited between 1991 and 1994 from the "Malmö Diet and Cancer" study. Normal BP was defined as if BP < 140/90 mmHg without pharmacological treatment for hypertension. Carotid artery atherosclerosis (CAA) was defined as CIMT ≥ 0.81mm or/and presence of plaque (i.e. focal CIMT>1.2 mm). The incidence of ischemic stroke was followed over a mean period 10.7 years.

Results

A total of 2228 subjects (791 men and 1437 women) had normal BP. During follow-up, 34 patients suffered a first-ever ischemic stroke (crude incidence: 1.51/1000 person-years). Prevalence of CAA in the subjects with and without stroke was 68.6% and 39.0%, respectively. It was estimated that the subjects with CAA had 3-fold higher risk for ischemic stroke (RR: 3.33, 1.37-8.14), independent of other cardiovascular risk factors. Each 1 standard deviation (0.13mm) increase in CIMT increased the stroke risk by 43% (RR: 1.43, 1.002-2.02). Several factors were found to have a notable relation with CAA, including age, male sex, smoking, diabetes, systolic BP, HbA1c and cholesterol.

Conclusions

Carotid IMT and atherosclerotic lesions are independent clinical markers for ischemic stroke among normotensive individuals.

Introduction

It is generally accepted that high blood pressure (BP) is the major risk factor for stroke (1-3). A large majority of stroke cases have been exposed to this causal risk factor. In unselected populations, however, approximately 10-20% of stroke events occur in subjects having normal BP (<140/90 mmHg) (4). Few researchers have paid attention to the risk of stroke in normotensive individuals (5,6).

In a large population-based study, the 'Malmö Diet and Cancer' (MDC) cohort, the risk of incident stroke has been investigated in the subjects with normal BP (6). A number of potential risk factors were found to be associated with incident stroke, including age, smoking, excess body weight, high-normal diastolic BP, history of ischemic heart disease and gastric ulcer (6). However, it is still unclear whether asymptomatic carotid atherosclerosis is associated with stroke in normotensive individuals.

Atherosclerosis has a long clinically silent phase lasting many years before the manifestation of overt disease. Carotid artery intima-media-thickness (CIMT) is considered as an early marker of arthrosclerosis. Increasing CIMT has been shown to increase the risk of incident stroke, after statistical adjustment for hypertension (7-11). However, hypertension is also a major determinant of CIMT (12) and it can be assumed that high CIMT often reflect previous exposure to hypertension (13-15). In this situation, statistical adjustment could be insufficient to fully account for the effects of hypertension on the relationship between CIMT and stroke. Analyses of normotensive individuals are also needed in order to fully explore the role of CIMT for incidence of stroke

The objective of this prospective study cohort was to investigate the impact of carotid artery atherosclerosis, defined by increased CIMT and/or carotid plaque, on the risk of first-ever ischemic stroke among the subjects who had a normal blood pressure.

Materials Methods

Study population

From 1991 to 1996, all men and women, born between 1923-1950 and living in the Malmö area in the southern part of Sweden, were recruited into the MDC study. Detailed information of the MDC study has been described previously (16). The cohort consists of 28449 subjects from the eligible population of about 74000 individuals. The detailed information about the participants has been described elsewhere (17).

A random 50% of participants who entered the MDC study between October 1991 and February 1994 were invited to take part in a study of the epidemiology of carotid artery diseases (18). In the total, 6103 subjects (2572 men and 3531 women) were examined by B-mode ultrasound of the right carotid artery and 5540 participants returned to donate blood samples for measurements of blood lipids and glucose status.

Subjects (n=2304) were included in the present study if they had a BP level <140/90 mmHg and were not on BP-lowering treatment. Subjects with history of stroke (n=17) or had incomplete ultrasound data (n=59) were excluded from the present analysis. Thus, the total study population consisted of 2228 subjects.

The ethical committee at Lund University approved the MDC study (LU 51-90). All subjects gave informed consent to participate.

Evaluation of atherosclerotic risk factors

Baseline characteristics

A self-administered questionnaire was used to obtain information on lifestyle (i.e. smoking habits, alcohol daily intake, physical activity), clinical information [history of

stroke, myocardial infarction (MI) and diabetes] and family history (father, mother and/or sibling) of cardiovascular disease (6). Body weight, waist and hip girth and blood pressure were measured as previous described (6). Presence of diabetes mellitus was certified if subjects reported the diagnosis in questionnaire, or was treated with anti-diabetic medication or had a fasting whole blood glucose ≥ 6.1mmol/L.

Carotid artery measurements

Participates underwent B-mode ultrasonography (Acuson 128 CT system, Mountain View, CA) of the right carotid artery. IMT of the common carotid artery and presence of carotid plaque were measured according to a standardized protocol by trained certified sonographers as previously published (18). In short, the bifurcation area of the right common carotid artery was scanned within a pre-defined 'window' comprising 3 cm of the right common carotid artery, the bifurcation, and 1 cm of the internal and external carotid artery, respectively, for the presence of plaque. IMT was determined in the far wall of the right distal common carotid artery according to the leading edge principle, using a specially designed computer-assisted analyzing system (19). IMT was then determined off-line as the mean wall thickness 1 cm proximal to the bifurcation. Each image was analysed without knowledge of the subject's identification code to minimize the possibility of observer bias. Methods of quality control have been published previously and been considered satisfactory (18).

In this study, two measures were adopted to estimate carotid artery atherosclerosis:

1) CIMT

The mean CIMT ≥ 0.81mm was considered as abnormal. The cut-point was based on the results issued from earlier publications within the MDC cohort (9,20). In these studies, a higher risk of MI and stroke was found in subjects with CIMT ≥ 0.81mm.

2) Atherosclerotic plaques

Presence of plaques within the pre-specified window of the right carotid artery was defined as a focal thickening of CIMT >1.2 mm (visually judged) (9). The numbers of plaques were classified as one plaque and two or more plaques.

Laboratory tests

After an overnight of fasting, blood samples were drawn to assess the profile of lipids [i.e. total cholesterol, low-density-lipoprotein (LDL) cholesterol, high-density-lipoprotein (HDL) cholesterol and triglycerides], HbA1c and glucose (21). Hypercholesterolemia was defined as fasting total cholesterol ≥ 6.5 mmol/L. The procedures of assessments were in accordance to the standard procedures at the Department of Clinical Chemistry, Malmö University Hospital.

Retrieval of endpoint

Record linkage with the National Inpatient Register, the Swedish Causes of Death Register and the Stroke Register of Malmö (STROMA) obtained information on morbidity and mortality from stroke in the MDC study (22). Information on case retrieval, validity and ascertainment of cases in the MDC has been described in detail previously (9,20). In short, every participant was followed from the baseline examination until incidence of stroke, death, or December 31, 2003. Stroke was defined as rapidly

developing clinical signs of local or global loss of cerebral function that lasted for > 24 hours or leading to death within 24 hours. Classification as subarachnoid (ICD-9, code 430) or intracerebral haemorrhage (ICD-9, code 431) required verification with computed tomography (CT) and/or autopsy. In this study, the subtype of cerebral infarction (ischemic, ICD-9, code 434) was the end point, which was diagnosed when CT or autopsy could verify the infarction and/or exclude haemorrhage and nonvascular disease. If neither imaging nor autopsy was performed, the stroke was classified as unspecified (ICD-9, CODE436). In subjects with more than one stroke event, only the first event was used for the analyses.

Statistical analyses

Logistic regression model was adopted to assess the risk of carotid artery atherosclerosis (CAA) (defined as CIMT ≥ 0.81mm or/and presence of plaque) in relation to baseline characteristics and laboratory tests. Cox-regression analyses with crude and covariate-adjustments were used to assess the incidence of ischemic stroke in relation to CIMT, presence of plaque and to CAA.

By using Kaplan-Meier method (23), the ischemic stroke-free survival rate was estimated in line with the category of CAA. Classification of CAA was defined as follows: CAA-0: CIMT < 0.81mm and absence of plaque; CAA-1: CIMT ≥ 0.81mm and absence of plaque and CAA-2: CIMT ≥ 0.81mm and presence of plaque.

All comparisons were two-sided and a 5% level of significance was used. The statistical analyses were conducted by the computer soft ware SPSS ^{TM} (11.5).

Results

In all, 2228 subjects (791 men and 1437 women) had a BP <140/90 mmHg and were not on BP-lowering treatment. The mean age at baseline examination was 55.7± 5.8 years.

Distribution of carotid artery atherosclerosis (CAA)

CIMT was 0.73mm ± 0.13mm (0.75±0.14 in men and 0.71±0.12 in women) and 23% had a CIMT level ≥ 0.81mm. Presence of carotid plaques was a common finding, affecting 25.7% of the subjects (28.9% in men and 23.8% in women) (Table 1). The prevalence of CAA was 39.5% (n= 879).

Incidence of ischemic stroke in relation to CAA

During a mean follow-up of 10.7±1.6 years (23965 person-years), 36 subjects suffered a first-ever stroke (crude incidence: 1.51/1000 person-years). Of them, 34 (94.4%) had cerebral infarction (ischemic), one had a subarachnoid hemorrhage and one had an unspecified stroke. In the present study, the cases with subarachnoid hemorrhage and unspecified subtypes were excluded from the analyses.

Among ischemic stroke cases, CAA at the baseline examination was found in more than two-thirds of the patients. Each 1 SD (0.13 mm) increase in CIMT increased the risk of stroke by 43% (RR 1.43, 1.002-2.02) (Table 2). It was observed that the crude rates of ischemic stroke and relative risks tended to increase in a linear fashion with increasing numbers of carotid plaques. In addition, the subjects who had CAA had a 3-fold higher risk (RR 3.60, 1.77-7.31) of ischemic stroke in comparison to the subjects without CAA (Table 2). This risk increase remained nearly unchanged when age, sex, smoking, systolic

BP, fasting glucose and LDL/HDL-cholesterol ratio were taken into account (RR 3.33, 1.37-8.14). Furthermore, it was also shown that the difference in ischemic stroke-free survival rates in relation to the severity of CAA increased continuously over time (age and sex adjusted *P* value for trend = 0.02) (Fig.1). The absolute risk associated with presence of CAA was more than 3-times higher in comparison to absence of CAA (2.6% vs. 0.8%. i.e. 23 events among 877 subjects and 11 in 1349, respectively).

Because of limited number of events a backward stepwise model was also performed. This model included CIMT (as a continuous variable), age, sex, smoking, systolic BP, fasting glucose and LDL/HDL- cholesterol ratio. Beside age, CIMT remained as a significant risk factor for an incident ischemic stroke. The same finding was observed when carotid plaques and CAA, respectively, were used.

Risk factors associated with CAA

By using logistic regression model with age and sex adjustments, the impact of baseline characteristics and laboratory parameters on the risk of CAA were examined (Table 3). Several factors were found significantly associated with presence of CAA, e.g. age, male gender, current smoking, presence of diabetes and systolic BP, HbA1c, fasting glucose, total and LDL-cholesterol. In addition, presence of CAA was inversely related to HDL-cholesterol.

Every third normotensive subject was found to have hypercholesterolemia. The age and sex adjusted odds ratio (OR) for CAA among subjects with hypercholesterolemia was 1.35 (1.10-1.65).

Discussion

Non-invasive imaging of the carotid artery, determined by B-mode ultrasonography, is increasingly used as a surrogate marker for assessing preclinical and clinical atherosclerosis in the general and high-risk populations (7,24). A strong association is observed between carotid atherosclerosis lesions and cardiovascular diseases, including MI and stroke (7,8,9,11,24).

To our knowledge, this is the first prospective population-based study investigating the risk of ischemic stroke in relation to carotid artery atherosclerosis in normotensive subjects. In this cohort, the signs of carotid atherosclerosis were observed in 39.5%. We found that for each 1 SD increase (0.13mm) in CIMT the risk of stroke increased significantly by 43% (95%CI:1-102%). This point estimate is compatible to the results from a recent meta-analysis based on 8 observational studies (7), in which the age and sex-adjusted overall estimates of the relative risk for incident stroke was 1.32 (1.27-1.38) per 1-standard deviation in CIMT difference. In addition, the incidence of ischemic stroke revealed a positive correlation with the grades of carotid plaques.

A combined measurement (CIMT $\geq$ 0.81mm or/and presence of plaque) was also utilized in this study to assess the impact of carotid artery atherosclerosis on stroke risk. We found that presence of CAA in normotensive subjects was associated with a 3-fold increased relative and absolute risks for ischemic stroke. This association was only marginally attenuated by other cardiovascular risk factors.

Although the presence of atherosclerotic lesions was shown to be an independent marker of ischemic stroke among normotensive subjects during 10-years follow-up, the absolute risk for ischemic stroke was 2.6%. It should be emphasized that the majority of subjects

with presence of carotid atherosclerosis remained event free, which may imply that carotid atherosclerotic lesion could be present in the asymptomatic stage for a long period. Thus, appropriate interventions through behavioral modification and clinical management in this silent stage may reverse or delay the harmful progression (25-27).

During the last decade, lipid-lowering therapy has been evidently proved to be effective in reversing the progression of carotid atherosclerosis (25-27). Lifestyle modification, lipid and BP-lowering therapy have been proven effective in slowing progression rate of CIMT (25-27). However, the greater benefits have been shown when combing the interventions (26).

Some methodological issues need to be addressed. In recent year, the measurements of carotid plaque area are considered as a stronger predictor for cardiovascular outcomes as compared to carotid IMT (28,29). In this study, however, it was impossible to obtain the information of carotid plaque area since the present investigation was operated in the early years of last decade. Lack of follow-up in carotid artery measurement and biological examinations is a limitation of this study. It is possible that carotid atherosclerosis may tend to deteriorate and the prevalence of hypertension and lipids disturbance may increase during the years of follow-up since those conditions are age related (30). The results might also be affected by changes in exposure of cardiovascular risk factors or medical intervention during follow-up.

The cut-point of CIMT used in this study for presence of carotid atherosclerosis might also be questioned as CIMT level might be influenced by the method of ultrasound measurements and furthermore by age, sex, ethnic group, etc (30-32). However, CIMT

was a risk factor for ischemic stroke also when it was used as a continuous variable. There is today no overall consensus how to standardize the measurement of CIMT and the definition of presence of carotid plaques (33,34). It was recommended recently by Mannheim CIMT consensus that CIMT measurements should be taken in areas free of lesions and that 'plaque should be defined as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value or demonstrates a thickness >1.5mm as measured from media-adventitia interface to intima-lumen interface' (33). According to the recommended definition, which has been questioned (34), the prevalence of carotid atherosclerosis in this cohort may be overestimated. However, our definition of CAA seems to be appropriate for the purpose of studying cardiovascular risk.

Summary

Carotid IMT and atherosclerotic lesions are independent clinical markers for ischemic stroke in subjects with normal blood pressure. Non-invasive assessment of carotid atherosclerosis seems to be a feasible method for tracking progression or early stage of atherosclerotic disease even in normotensives.

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Tables

Table 1, Distribution of carotid artery atherosclerosis among normotensive subjects.

	Normotensives (n= 2228)
Age (years), mean ± SD	55.7 ± 5.8
Male-sex, %	35.5
Carotid intima-media thickness (mm)	
Mean ± SD	0.73 ± 0.13
Mean ± SD (maximum)	0.89 ± 0.16
Carotid intima-media thickness >0.81mm, %	23.3
Presence of carotid plaque	
no, %	74.3
one plaque, %	18.7
two or more plaques, %	7.0
Presence of CAA †, %	39.5

† CAA was defined as CIMT ≥ 0.81 or/and presence of plaque (i.e. focal CIMT>1.2mm).

Table 2, Incidence of ischemic stroke in relation to carotid IMT, carotid plaque and CAA in normotensive subjects.

	Cases / Subjects	Incidence per	Relative risk, 95%CI	
	no.	1000 person-years	Crude	Covariate-adjusted †
CIMT				
(per SD 0.13mm increase)			1.60 (1.22-2.10)	1.43 (1.002-2.02)
Carotid plaque ‡				
no	17 / 1606	1.04	1.0	1.0
one plaque	9 / 404	2.12	2.06 (0.92-4.58)	1.80 (0.69-4.68)
two or more plaques	8 / 152	4.91	4.74 (2.06-10.90)	3.77 (1.41-10.08)
CAA #				
no	11 / 1349	0.76	1.0	1.0
yes	23 / 877	2.69	3.60 (1.77-7.31)	3.33 (1.37-8.14)

† RRs were adjusted for age, sex, smoking, systolic BP, fasting blood glucose and LDL/HDL-cholesterol ratio.

‡ Information on carotid plaque was unavailable in 64 subjects.

CAA was defined as CIMT ≥ 0.81 or/and presence of plaque.

Table 3, Carotid artery atherosclerosis (CAA) in relation to baseline characteristics among normotensive subjects.

	CAA		
	No (n= 1349)	Yes (n= 879)	Odds Ratio (95%CI) †
Subject demographics			
Age, years	54.5 ± 5.5	57.5 ± 5.7	1.10 (1.08-1.11)
Male sex, %	32.5	41.5	1.54 (1.29-1.85)
Baseline risk factors			
Current smoking, %	23.1	33.1	1.88 (1.53-2.32)
Alcohol intake (grams per day) ‡, %	6.91 (11.81)	6.17 (11.49)	0.99 (0.98-1.003)
Low physical activity, %	25.7	24.3	1.03 (0.88-1.29)
Presence of diabetes, %	2.6	5.2	1.71 (1.06-2.76)
History of myocardial infarction, %	0.8	2.5	1.80 (0.82-3.95)
Family history of CVD, %	47.4	48.3	0.86 (0.70-1.07)
Physical examinations			
Systolic BP, mmHg	123 ± 8	125 ± 8	1.01 (1.002-1.03)
Diastolic BP, mmHg	79 ± 5	79 ± 5	1.00 (0.98-1.02)
Waist circumference, cm	79.3 ± 11.0	81.1 ± 11.5	1.00 (0.99-1.01)
BMI, kg/m^2	24.6 ± 3.32	24.6 ± 3.26	0.99 (0.97-1.02)
Laboratory tests			
HbA1c, %	4.74 ± 0.53	4.88 ± 0.61	1.25 (1.06-1.49)
Fasting glucose, mmol/L	4.85 ± 0.77	4.99 ± 1.09	1.12 (1.006-1.25)
Triglycerides, mmol/L ‡	1.02 (0.58)	1.10 (0.67)	1.13 (0.97-1.32)
Total cholesterol, mmol/L	5.94 ± 1.07	6.19 ± 1.07	1.15 (1.05-1.26)
HDL-cholesterol, mmol/L	1.46 ± 0.37	1.38 ± 0.36	0.57 (0.43-0.76)
LDL-cholesterol, mmol/L	3.95 ± 0.96	4.23 ± 0.98	1.23 (1.11-1.36)
LDL/HDL-cholesterol Ratio	2.9	3.3	1.28 (1.17-1.39)

Unless otherwise indicated, figures are presented as mean ± SD.

† Odds ratios were adjusted for age and sex (except age or sex itself).

‡ Log-transformed before the statistical analyses because of skewed distributions; data presented as median with the interquartile range in parentheses.

8, Figure legends

Fig. 1, Stroke-free survival in relation to the degree of carotid artery atherosclerosis (CAA) among normotensive subjects (n=2228).

(Age-sex-adjusted *P* value for trend = 0.02)

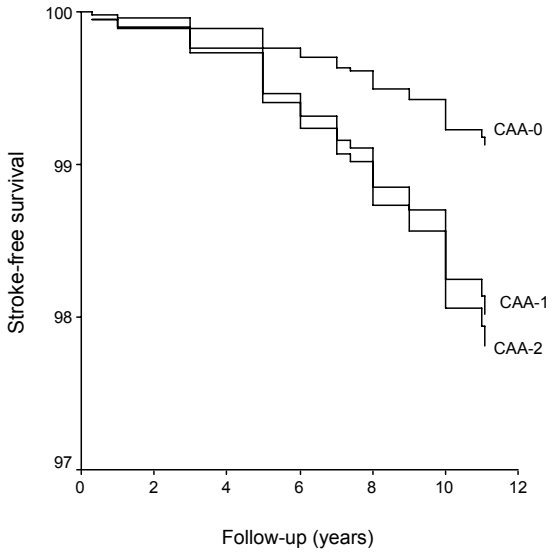
Note:

CAA-0: carotid IMT < 0.81mm and without plaque;

CAA-1: carotid IMT ≥ 0.81mm and without plaque;

CAA-2: carotid IMT ≥ 0.81mm and presence of plaque.

Fig.1


100
99
98
97
Stroke-free survival
0
2
4
6
8
10
12
Follow-up (years)
CAA-0
CAA-1
CAA-2