Atherosclerotic carotid artery disease and white matter disease in subjects without a history of cerebral infarction or transient cerebral ischemia

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Abstract

Introduction: Atherosclerotic carotid artery disease (CAD) is a major risk factor for cerebrovascular disease. **Objective:** To analyze the association of major vascular risk factors with atherosclerotic CAD and white matter disease (WMD) in patients without a history of ischemic stroke. **Method:** Risk factors were assessed with carotid examination using Doppler duplex ultrasound. Cases with a history cerebral infarction or transient ischemic attack were not included. Subjects had brain magnetic resonance imaging scans available and those with large-artery ischemic lesions were excluded. Multivariate models were constructed for the prediction of atherosclerotic CAD, significant carotid stenosis, atheroma burden and WMD. **Results:** One-hundred and forty-five subjects were assessed (60.7% were females, mean age was 73 years). Atherosclerotic CAD was documented in 54.5%, carotid stenosis $\geq 50\%$ in 9.0%, > 6 atheroma plaques in 7.6%, and periventricular or sub-cortical WMD in 28.3% (20.6% had atherosclerotic CAD and WMD concurrently). Risk factors independently associated with atherosclerotic CAD were age and hypertension; hypertension was associated with $\geq 50\%$ carotid stenosis; age was associated with > 6 atheroma plaques; and age, diabetes and hypertension were associated with WMD. Obesity was not associated with any of the analyzed independent variables. **Conclusions:** In asymptomatic subjects without a history of ischemic stroke, age and hypertension were the most important risk factors for macrovascular disease. Diabetes mellitus was associated with microvascular disease. Obesity alone was not a major determinant of CAD or WMD.

KEY WORDS: Atherosclerosis. Diabetes. Carotid artery disease. Hypertension. White matter disease. Obesity.

Introduction

Moderate to severe atherosclerotic carotid artery disease (CAD) has a prevalence of 0.3 to 6 % in asymptomatic general population, depending on age and gender.¹⁻⁵ This frequency can be markedly increased in subjects with cardiovascular risk factors, but especially in those with a history of atherothrombotic disease, and thus, in high-risk groups, CAD can

be documented in approximately 80 % of cases, according to the group under study.⁶⁻¹²

Clinically significant CAD can be defined according to the degree of stenosis, arterial wall thickening, atheroma plaque load or dimensions, which depends on the method used to document the CAD (carotid ultrasound, tomography, magnetic resonance, autopsy, among others).^{2,4,12} In the general population, clinically significant CAD is more common due to plaque

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rather than stenosis by $> 50\%$.¹ Despite its low relative frequency, CAD is the cause of up to 30 % of ischemic stroke cases (cerebral infarction or transient ischemic attack).^{2,6,7,10,11} Moreover, the frequency of atheromatous and atherothrombotic disease in other arterial beds of subjects who suffer from CAD is very high,¹³ as well as mental function impairment,¹⁴ hence CAD clinical importance going beyond its causal relationship with ischemic stroke.

The relationship of traditional and emerging risk factors with CAD in asymptomatic individuals without a history of stroke has been difficult to define owing to the methodology used to characterize CAD, the model of epidemiological study and the collection of variables. Recently, risk factors such as hypertension, diabetes mellitus, smoking and dyslipidemia have been documented to be more important in their relationship with asymptomatic CAD than obesity itself.^{7,12,15,16} Our objective was to describe the relationship of traditional risk factors with CAD in individuals without a history of stroke.

Method

Retrospective study of patients referred for carotid ultrasonographic examination to the “Salvador Zubirán” National Institute of Medical Sciences and Nutrition, in Mexico City. Selected patients met the following criteria:

- Adults of either gender
- Ultrasonographic carotid evaluation for a reason other than the search for cerebrovascular disease etiology
- No personal history of hemorrhagic or ischemic stroke (cerebral infarction or transient ischemic attack)
- Having a brain magnetic resonance imaging (MRI) study obtained six months prior or after the performance of the carotid ultrasound.

Cases were excluded if any of the following criteria was documented:

- Physical examination with focal neurologic signs
- Dementia
- Neuroimaging studies with cortical-subcortical lesions typical of large vessel occlusion stroke.

The research and research ethics committees of the center approved this study. A standardized physical capture instrument was used to collect the data that made up an electronic database. Demographic characteristics, cardiovascular risk factors, medical treatments and cervical artery duplex ultrasonography characteristics were obtained from medical records.

Significant stenosis was defined as the presence of atheroma plaque in the internal carotid causing $\geq 50\%$ stenosis.^{4,6,7} The carotid ultrasonography of each patient was examined to characterize the atheroma plaque load and the degree of stenosis identifiable by this method. Plaque load was categorized according to their number: mild, one to three plaques; moderate, four to six plaques and severe, ≥ 7 plaques.

CAD was defined as the presence of any of the following characteristics: one or more atheroma plaques, carotid intima-media thickness ≥ 1 mm or carotid stenosis $\geq 50\%$.

In addition, imaging variables, such as white matter disease, its distribution and extension, were collected by brain magnetic resonance imaging (MRI). Cases where potential ischemic lesions were identified were excluded. White matter disease was defined as the presence of signal strength increase on T2 and FLAIR sequences in periventricular or subcortical regions.

Nominal variables simple relative frequencies are expressed as proportions, and age as the median with its interquartile range, since it had no normal distribution. To compare nominal variables frequencies between two or more groups, Pearson's chi-square test was used. Non-parametric quantitative variables' medians were compared between two groups using Mann-Whitney's U-test. Multivariate models were constructed by binary logistic regression to identify risk factors potentially associated with significant carotid stenosis, atheroma plaque load and white matter disease on MRI, with variables associated with the dependent variable in the bivariate analysis being selected for this purpose, with a p-value < 0.20 . The results of the multivariate analysis were recorded with the odds ratio (OR) and its 95 % confidence intervals (CI). To assess the reliability of the models, the Hosmer and Lemeshow goodness of fit test was used; it was considered to be adequate when a p-value > 0.20 was obtained. All p-values for comparisons were calculated with two tails and were considered significant when they were < 0.05 . SPSS statistical package, version 24.0, was used for all calculations.

Results

Out of 194 initially selected patients, 49 were excluded after applying the selection criteria. Thus, 145 patients were included in the final analysis (60.7 % of females, median age: 73 years, interquartile range = 63-81 years. The reasons why carotid duplex ultrasonography and neuroimaging were performed

Table 1. Bivariate analysis of major vascular risk factors associated with carotid and small vessel diseases*

Risk factors	Carotid disease				p	Small vessel disease				p
	Without (n = 66)		With (n = 79)			Without (n = 104)		With (n = 41)		
	Median	IQR	Median	%		Median	%	Median	IQR	
Age in years	67	56-77	76	69-83	< 0.001	69	60-77	81	74-84	< 0.001
	n	%	n	%		n %	%	n	%	
Female gender	39	59.1	49	62.0	0.719	58	55.8	30	73.2	0.053
BMI ≥ 27	21	31.8	27	34.2	0.764	36	34.6	12	29.3	0.538
BMI ≥ 30	12	18.2	12	15.2	0.629	18	17.3	6	80.5	0.696
Hypertension	31	47.0	60	75.9	< 0.001	58	55.8	33	80.5	0.006
Hypercholesterolemia	26	39.4	40	50.6	0.176	45	43.3	21	51.2	0.387
Hypertriglyceridemia	18	27.3	23	29.1	0.806	28	26.9	13	31.7	0.565
Mixed dyslipidemia**	17	25.8	19	24.1	0.813	25	24.0	11	26.8	0.726
Diabetes	16	24.2	36	45.6	0.008	30	28.8	22	53.7	0.005
Smoking ***	27	40.9	32	40.5	0.961	42	40.4	17	41.5	0.905
Ischemic heart disease	4	6.1	10	12.7	0.180	9	8.7	5	12.2	0.516
Non-valvular atrial fibrillation	1	1.5	6	7.6	0.089	4	3.8	3	7.3	0.380

*Atherosclerotic carotid disease defined here as any of the following: one or more atheroma plaques, carotid intima-media thickness $\geq$ 1 mm or $\geq$ 50% carotid stenosis. White matter disease characterized on magnetic resonance by increased signal intensity on T2 and FLAIR sequences in periventricular or subcortical regions.

**Hypercholesterolemia and hypertriglyceridemia.

*** Current or former smokers. IQR=interquartile range.

were syncope (63 %), mild cognitive impairment or memory impairment (22 %), rheumatologic disease (8 %), ischemic heart disease (2 %) assessment and other reasons (5%). No patient included in the final database had a history of ischemic stroke, physical examination with focal neurologic signs or neuroimaging with large vessel ischemic lesions.

The most common risk factors were age $\geq$ 65 years (n = 103, 71 %), hypertension (n = 91, 62.8 %), hypercholesterolemia (n = 66, 45.5 %), smoking (n = 59, 40.7 %), diabetes mellitus (n = 52, 35.9 %) and obesity (n = 48, 33.1 %). Risk factor distribution was comparable between men and women, except for smoking (56.1 and 30.7 %, respectively; p = 0.002), arterial hypertension (52.6 and 69.3 %, p = 0.042) and diabetes mellitus (29.5 and 45.6 %, p = 0.049).

The prevalence of CAD was 54.5 % (n = 79), $\geq$ 50 % carotid stenosis, 9.0 % (n = 13) and periventricular or subcortical leukopathy on MRI, 28.3 % (n = 41); 30 patients (20.7 %) had CAD and leukopathy concurrence, i.e., 73.1% of total sample had leukopathy. The frequency of CAD between men and women was not different (55.7 and 52.6 %, p = 0.719), and neither was for carotid stenosis $\geq$ 50 % (7.0 and 10.2 %, p = 0.509)

or leukopathy (19.3 and 34.1 %, p = 0.053). However, the prevalence of CAD coexistence with leukopathy was significantly higher in women (26.1 %) than in men (12.3 %) (p = 0.044).

In the bivariate analysis, age, hypertension and diabetes were identified as risk factors associated with CAD, and as potentially associated, hypercholesterolemia, ischemic heart disease and atrial fibrillation (Table 1). Factors associated with leukopathy were age, hypertension and diabetes and, potentially, the female gender. Statistically significant and potential risk factors (p < 0.20) were used to construct multivariate models for the prediction of CAD, $\geq$ 50 % carotid stenosis and atheroma plaque load > 6 (Table 2). This is how age and hypertension were identified as independent risk factors for CAD, hypertension as the only independent factor associated with $\geq$ 50 % carotid stenosis and age as the only independent factor of high atheromatous load prediction. In the white matter disease prediction model, age, diabetes and hypertension were identified as independent variables for the prediction of risk (Table 3). These same variables were independently associated with leukopathy concurrence with CAD (Table 4).

Table 2. Large vessel disease: multivariate models for vascular risk factors associated with carotid stenosis, atheroma load and white matter disease (n = 194)

Model	Variable	OR (95 % CI)	p
Model for atherosclerotic carotid artery disease*	Age**	1.070 (1.035-1.106)	< 0.001
	Hypertension	3.628 (1.681-7.830)	0.001
Model for moderate to severe carotid stenosis***	Hypertension	8.051 (1.016-63.766)	0.048
Model for > 6 atheroma plaques†	Age**	1.136 (1.044-1.237)	0.003

*Atherosclerotic carotid artery disease defined as any of the following: one or more atheroma plaques, carotid intima-media thickness ≥ 1 mm or $\geq 50\%$ carotid stenosis.

Hosmer-Lemeshow goodness of fit test in last step: $\chi^2 = 5.094$, 2 df, $p = 0.748$. Model adjusted for age, gender, diabetes, hypertension, obesity, smoking, hypercholesterolemia, hypertriglyceridemia, atrial fibrillation, personal history of ischemic heart disease and family history of atherothrombotic events.

**Age for each year of increase.

*** $\geq 50\%$ carotid stenosis. Hosmer-Lemeshow goodness of fit test in last step: $\chi^2 = 3.473$, 1 df, $p = 0.812$. Model adjusted for age, gender, diabetes, hypertension, obesity, smoking, hypercholesterolemia, hypertriglyceridemia, atrial fibrillation, personal history of ischemic heart disease and family history of atherothrombotic events.

†Hosmer-Lemeshow goodness of fit test in last step: $\chi^2 = 3.468$, 1 df, $p = 0.839$. Model adjusted for age, gender, diabetes, hypertension, obesity, smoking, hypercholesterolemia, hypertriglyceridemia, atrial fibrillation, personal history of ischemic heart disease and family history of atherothrombotic events.

Table 3. Small vessel disease: multivariate model for risk factors associated with white matter disease in individuals without a history of ischemic stroke (n = 194)

Model	Variable	OR (95 % CI)	p
Model for white matter disease on magnetic resonance*	Age**	1.121 (1.066-1.179)	0.002
	Diabetes mellitus	2.425 (1.035-5.681)	0.005
	Hypertension	3.896 (1.416-10.719)	0.005

*White matter disease on magnetic resonance characterized by increased signal intensity on T2 and FLAIR sequences in periventricular or subcortical regions.

Hosmer-Lemeshow goodness of fit test in last step: $\chi^2 = 2.752$, 3 df, $p = 0.907$. Model adjusted for age, gender, diabetes, hypertension, obesity, smoking, hypercholesterolemia, hypertriglyceridemia, atrial fibrillation, personal history of ischemic heart disease and family history of atherothrombotic events.

**Age for each year of increase.

Table 4. Coexistence of large and small vessel disease: multivariate model for risk factors associated with carotid atheromatous disease and white matter disease concurrence in individuals without a history of ischemic stroke (n = 194)

Model	Variable	OR (95 % CI)	p
Model for carotid atheromatous disease and white matter disease concurrence*	Age**	1.114 (1.052-1.179)	< 0.001
	Diabetes mellitus	3.967 (1.533-10.268)	0.005
	Hypertension	6.090 (1.728-21.468)	0.005

*Carotid atheromatous disease defined as any of the following: one or more atheroma plaques, carotid intima-media thickness ≥ 1 mm or $\geq 50\%$ carotid stenosis.

White matter disease on magnetic resonance characterized by increased signal intensity on T2 and FLAIR sequences in periventricular or subcortical regions.

Hosmer-Lemeshow goodness of fit test in last step: $\chi^2 = 2.890$, 3 df, $p = 0.941$. Model adjusted for age, gender, diabetes, hypertension, obesity, smoking, hypercholesterolemia, hypertriglyceridemia, atrial fibrillation, personal history of ischemic heart disease and family history of atherothrombotic events.

**Age for each year of increase.

Discussion

CAD is clinically divided into stenosing and non-stenosing according to the degree of vessel lumen reduction.^{17,18} Although stenosing CAD is the carotid pathology that is most causally associated with ischemic stroke, it is essential to consider that atherosclerosis indicates an unhealthy artery and that quite often it is related to atheromatous disease in other arterial beds,^{12,15,19} which can lead to confusion in the medical literature and in routine clinical practice, when mistakenly considering an artery without stenosis as being normal.^{20,21} CAD, even in its non-stenosing form, is a known risk marker for both ischemic stroke and death

due to atherothrombotic events.^{19,22-26} Therefore, it is important to identify the relationship between vascular risk factors and CAD different dimensions or characteristics, especially in individuals without a history of stroke, in order to avoid wrong conclusions resulting from the reverse causality phenomenon when studying only patients with stroke secondary to large vessel disease.

As the present study has demonstrated, CAD is in turn associated in different ways with so-called “major” traditional risk factors, depending on the criterion or atheromatous disease characteristics.^{1,9,14,25-29} A similar case can be described in brain white matter disease (e.g., leukopathy or leukoaraiosis), as defined

by tomography or MRI and according to characteristics of its distribution and extension.²⁹⁻³¹ As it has been reported,¹⁻¹⁴ in the present analysis obesity was not found to be an independent risk factor for CAD or leukopathy. It is possible that obesity is more causally related to dyslipidemia, diabetes or hypertension than directly to macro- and microvascular disease. It is also possible that this study failed to demonstrate a direct and independent association between obesity and arteriopathy owing to a limited statistical power, or because body mass index (BMI) is not an ideal anthropometric adiposity marker, as currently recognized.³²⁻³⁴ In our series, the most important risk factor was hypertension, which is consistent with previous reports,²⁵⁻³¹ while diabetes was a risk factor that was more closely associated with cerebral microangiopathy, at least in our study group.

Interestingly, although previously CAD and small vessel disease were considered not to be linked,³⁵ now it is known that not only do they share risk factors, but both entities often coexist.^{32,35} It is important noting that risk factor distribution in low-risk populations (e.g., general or asymptomatic population) tends to differ between different ethnic groups while it is relatively homogeneous when high-risk populations are studied (e.g., subjects with atherothrombotic events).^{1,10,14,36} Thus, it is possible that the identified risk factors may differ from those of other groups of asymptomatic individuals.

This study has potential limitations that should be noted, with the most significant being the relatively small sample size for the detection of risk factors whose frequency is low, but whose causal association could be high for the development of macro- and microangiopathy. On the other hand, the retrospective nature of the study might involve selection biases, considering the medical indications that motivated the performance of ultrasonography and neuroimaging studies.

Being a cross-sectional study, it has not been possible to evaluate the implication of macro- and microvascular disease markers with relevant clinical outcomes, such as ischemic stroke, major cognitive impairment and cardiovascular death. Moreover, although care was taken to select asymptomatic subjects, given that they were non-voluntary patients and participants of a referral institution, they cannot be considered to be representative of the general asymptomatic population.

Notwithstanding the above, this analysis provides useful information for generating new scientific hypotheses,

provides essential data for the calculation of the samples of upcoming studies and supports in clinical decision-making, particularly regarding the search for arterial and metabolic disease among subjects who have CAD or vascular leukopathy.

In conclusion, in this group of asymptomatic subjects with no history of acute cerebrovascular disease, age and hypertension were the most important risk factors related to macrovascular disease imaging. Diabetes mellitus was more closely associated with microvascular disease and obesity per se was not a major determinant of CAD or cerebral microangiopathy.

Declarations of potential conflicts of interests

There was no affiliation with organizations with a direct or indirect monetary or ethical interest with the subject matter discussed in this scientific manuscript, all authors therefore declare to have no conflicts of interest that might have affected the design of the study and the report of its results.

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