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Carotid Atherosclerotic Markers in CADASIL

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Key Words
Atherosclerosis · Carotid atherosclerosis · CADASIL · Carotid duplex ultrasonography · *NOTCH3* gene

Abstract
Purpose: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a cerebral small vessel disease caused by mutations of the *NOTCH3* gene. Marked variations in disease severity have raised the hypothesis that non-genetic factors may modulate the expressivity of the phenotype. The aim of the current study was to evaluate whether atherosclerosis, assessed by carotid duplex ultrasonography, is associated with variations in the clinical and MRI phenotype of CADASIL. ***Methods:*** Data from 144 consecutive patients enrolled in an ongoing prospective cohort study were collected. Degree of disability was assessed by the modified Rankin Scale, that of cognitive impairment by the Mattis Dementia Rating Scale (MDRS). The total volume of the brain, of lacunar lesions and of white matter hyperintensities, the number of cerebral microhemorrhages, and parameters derived from histograms of apparent diffusion coefficient were measured on cerebral MRI. Atherosclerosis was evaluated by B-mode ultrasonography of carotid arteries. Both the carotid intima-media thickness (cIMT) and the presence of carotid plaques or stenosis were recorded. ***Results:*** Higher cIMT was found to be independently associated with lower MDRS scores when this score was less than the quartile limit ($p = 0.02$). Only a trend for a positive association was detected between cIMT and the Rankin score ($p = 0.06$). There was no significant association between carotid markers and the occurrence of stroke or MRI parameters except for diffusion data. The mean and peak values of MRI diffusion histograms were found positively associated with the presence of plaques ($p < 0.01$). ***Conclusion:*** The results suggest that the severity of atherosclerosis may relate to cognitive decline in CADASIL and that this effect is possibly related to the degree of microstructural cerebral tissue lesions. Longitudinal studies are needed to confirm these results.

Introduction

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a small vessel disease of the brain caused by mutations in the *NOTCH3* gene [1]. The clinical hallmarks of CADASIL include attacks of migraine with aura, recurrent lacu-

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nar stroke, mood disturbances and progressive subcortical dementia [2–4].

To date, with the exception of rare mutations in the EGFR10-11 domain that may affect the clinical expression of the disease, no obvious genotype/phenotype has been demonstrated [5–7]. However, some data suggest that classical vascular risk factors may influence the outcome in CADASIL. In a previous series, Singhal et al. [5] found that active smoking was associated with younger age at first ischemic manifestation. In a cross-sectional study, Viswanathan et al. [8] recently observed that higher levels of HbA_{1C} and systolic blood pressure were related to the number of cerebral microhemorrhages on gradient-echo imaging. Recently, Adib-Samii et al. [9] reported that hypertension and smoking were associated with an increased risk of stroke in 200 CADASIL patients.

In the general population, the carotid intima-media thickness (cIMT) and the presence of carotid plaques evaluated by duplex ultrasonography are considered as early markers of atherosclerosis and have been associated with the severity of systemic atherosclerosis [10, 11]. They are also independent predictors of both cardiovascular and cerebrovascular events [12, 13]. Moreover, cIMT has been associated with white-matter hyperintensities on T_2-weighted MRI and with cognitive decline in elderly people as were arterial stiffening and endothelial dysfunction [14]. Whether the severity of atherosclerosis can modulate the expression of a specific small vessel disease not related to the current vascular risk factors remains unknown.

In the present study, we hypothesized that atherosclerosis assessed by carotid duplex ultrasonography might have an impact on the clinical or brain MRI phenotype of CADASIL.

Subjects and Methods

Subjects

Subjects were drawn from an ongoing prospective cohort study of consecutive patients with CADASIL in Lariboisière Hospital, Paris, between June 2003 and November 2006. Complete study design has been detailed elsewhere [8, 15]. In summary, in 144 genetically confirmed CADASIL patients, clinical and demographic data were collected. They underwent a general and neurological examination, including an evaluation of the degree of disability based on the modified Rankin Scale (mRS) (poor outcome was defined as mRS $\geq$3). Neuropsychological evaluation with the Mattis Dementia Rating Scale (MDRS) [16] was also performed. The educational level was assessed with a scale from 1 (illiterate) to 7 (university diploma). Note that history of hypertension was defined as previous diagnosis of hypertension (>140/90) or use of antihypertensive treatment for control of blood pressure.

All patients had cerebral MRI and cervical ultrasound examination. All patients had blood drawn for laboratory screening including: complete blood count, glucose, hemoglobin A_{1c} (HbA_{1c}), cholesterol panel, triglycerides, homocysteine, fibrinogen and CRP.

Informed consent was obtained from each subject or from a relative if the patient was not able to give written consent. The study was approved by an independent ethic committee.

Magnetic Resonance Imaging

Cerebral MRI scans were obtained by the use of a 1.5-T system (Signa General Electric Medical Systems). 3D T_1-weighted sequences, fluid-attenuated inversion recovery (FLAIR), T_2*-weighted gradient-echo planar and diffusion-weighted imaging were performed. The methods used for MRI analysis and the validation of the different measurements have been detailed elsewhere [8, 15].

White matter hyperintensities (WMH) lesions were analyzed on FLAIR images. The total volume of WMH was normalized to the intracranial cavity (ICC) in each patient [normalized volume of WMH or nWMH = (volume of WMH/volume ICC) · 100]. To assess the total volume of lacunes, all hypointense lesions with both a signal identical to that of cerebrospinal fluid and a diameter >2 mm were selected. The total volume of lacunes in each patient was normalized to the ICC [normalized lacunar volume or nLV = (volume of lacunes/volume ICC) · 100]. Microhemorrhages were defined as rounded foci $\leq$5 mm in diameter hypointense on gradient-echo sequences and distinct from vascular flow voids, leptomeningeal hemosiderosis, or non-hemorrhagic subcortical mineralization. The number of microhemorrhages was recorded in each patient. Histograms of apparent diffusion coefficient (ADC) values from ADC maps were generated for each patient using a bin width equal to 0.1×10^{-4} mm^2 s^{-1}. Voxels containing cerebrospinal fluid were excluded in all patients before calculation using a superior threshold value at 27×10^{-4} mm^2 s^{-1}. To correct for cross-subject differences in brain volume, each histogram was normalized to the total number of brain tissue voxels. Both the mean ADC and diffusion value at the peak (peak value) derived from each histogram were used for analysis. Due to small changes in diffusion values after the upgrade of the MR device and coils that occurred during the study, the analysis of diffusion data was restricted to the 104 patients who had their examination before the upgrade. Determination of global brain volumes from 3D T_1 sequences was performed using the BrainVISA software (CEA, Orsay, France; http://brainvisa.info) as previously detailed [17]. Brain parenchymal fraction (BPF) was defined as the ratio of brain tissue volume to total intracranial cavity volume (BPF = brain tissue volume/ICC).

Ultrasonography

Participants had a cervical ultrasound B-mode examination (Acuson, 7-MHz probe) performed at inclusion. All examinations were performed by trained physicians. Longitudinal and cross-sectional ultrasound images were taken bilaterally throughout the extracranial portion of the common carotid artery (CCA) and of the bifurcation and origin of the internal carotid artery bilaterally. Plaque was defined as a focal structure encroaching into the lumen of at least 0.5 mm or a thickening $\geq$1.5 mm (distance between media-adventitia interface to the intima-lumen interface) and stenosis was defined as a plaque of more than 20% of the lumen axe in cross section [18]. Carotid atherosclerosis lesions were

Table 1. Logistic regression according to the presence of carotid plaques or stenosis and linear regression with cIMT

Variable	Plaques (n = 48/144 patients)				cIMT (n = 134 patients)		
	univariate analysis		multivariate analysis		univariate analysis		multivariate analysis
	OR [95% CI]	p value	OR [95% CI]	p value	Pearson correlation coefficient	p value	p value
Age (10-year increase)	2.34 [1.60; 3.44]	<0.0001	2.49 [1.64; 3.79]	<0.0001	0.644	<0.0001	<0.0001
Sex (male vs. female)	2.80 [1.36; 5.78]	0.0053	3.11 [1.39; 6.97]	0.0059	0.149	0.0852	
Educational level	1.17 [0.94; 1.47]	0.1559			–0.294	0.0007	0.0034
History of high blood pressure (yes vs. no)	1.52 [0.62; 3.74]	0.3590			0.039	0.6529	
History of hypercholesterolemia (yes vs. no)	1.70 [0.84; 3.42]	0.1385			0.086	0.3225	
History of diabetes (yes vs. no)	0.99 [0.09; 11.19]	0.9931			–0.107	0.2201	
Current or ex-smoker (yes vs. no)	1.26 [0.63; 2.53]	0.5149			0.021	0.8091	
SBP, mm Hg	1.02 [1.00; 1.04]	0.0297			0.102	0.2527	
DBP, mm Hg	1.01 [0.98; 1.04]	0.5364			0.039	0.6613	
BMI	0.98 [0.90; 1.07]	0.6598			0.052	0.5901	
HDL, mmol/l	0.72 [0.30; 1.74]	0.4662			–0.026	0.7777	
LDL, mmol/l	1.22 [0.85; 1.76]	0.2775			0.106	0.2223	
Total cholesterol, mmol/l	1.18 [0.89; 1.57]	0.2434			0.103	0.2367	
Triglycerides, mmol/l	2.00 [1.10; 3.63]	0.0223			0.140	0.1070	
Glycated hemoglobin	1.29 [0.63; 2.65]	0.4882			0.084	0.3355	
Blood glucose, mmol/l	0.98 [0.70; 1.38]	0.9047			–0.027	0.7577	
Homocysteine, μmol/l	1.03 [0.95; 1.11]	0.5136			0.168	0.0551	
CRP, mg/l	1.00 [0.95; 1.05]	0.9374			0.099	0.2542	
Fibrinogen, g/l	1.48 [0.91; 2.40]	0.1125			0.315	0.0003	

classified as either no plaque or presence of plaque or stenosis. As recommended, the near and far walls of the middle parts of the right and left CCA were scanned longitudinally to assess the best angle of incidence for cIMT measurements. Then an average cIMT measurement was performed on a 10-mm segment at the far wall of each CCA using dedicated software (M'Ath®-Std©). The average of right and left CCA IMT measurements was used for analysis. The inter- and intrarater reliability was not calculated in the present study but was previously assessed in large studies and was found to be good [19].

Statistical Methods

Analyses were conducted using SAS® software v.9.1 (SAS Institute Inc., Cary, N.C., USA). Data are summarized as frequencies and percentages for categorical data and as mean and standard deviation for continuous variables. Odds ratios (OR) are reported with 95% confidence intervals (95% CIs).

First analysis was performed to identify factors associated with carotid plaques or stenosis and with cIMT among the following variables: age, sex, educational level, history of hypertension, history of hypercholesterolemia, history of diabetes, smoking status, systolic blood pressure, diastolic blood pressure, body mass index, HDL, LDL, total cholesterol, triglycerides, HbA_{1C}, blood glucose, homocysteine, CRP, and fibrinogen level.

The second analysis used the same procedure to identify correlations between clinical and radiological markers of CADASIL by adding either carotid plaque or stenosis and cIMT among the evaluated factors.

For binary endpoints (presence of carotid plaques or stenosis, presence of stroke, disability, cognitive impairment and microhemorrhages), univariate logistic regressions were first performed. Variables statistically significant at a 15% threshold in the univariate analysis were then introduced into a multivariable stepwise logistic regression to identify independent correlates of these endpoints. Validity of all models was evaluated by the bootstrapping procedure (n = 1,000 bootstrap samples).

For the continuous measures (cIMT, extent of white matter lesions, total volume of lacunes, BPF and mean ADC), Pearson correlation coefficients were obtained, and multivariable stepwise linear regressions were used to find the linear models that best predict continuous measures. Resampling procedures were used for validation of these models. The significance level was fixed at 5%.

Results

Main Cohort Characteristics

The mean age in the cohort was 52.6 ± 11.9 years (median 52.8, range 24.1–77.5) and 72 men (50%) were included. Ninety-three subjects (64.6%) had at least one ischemic stroke before inclusion and 32 (22.2%) had a mRS ≥3. The median MDRS score was 140 and its lower quartile limit was 127. The frequency of vascular risk factors was as follows: history of hypertension (n = 24/144 subjects, 16.7%),

Table 2. Logistic regression using MDRS score at 140 or at 127 as cutoff values for the presence of cognitive impairment

Variable	MDRS ≤140 (n = 68/130 patients)				MDRS ≤127 (n = 35/130 patients)			
	univariate analysis		multivariate analysis		univariate analysis		multivariate analysis	
	OR [95% CI]	p value	OR [95% CI]	p value	OR [95% CI]	p value	OR [95% CI]	p value
cIMT (0.05-mm increase)	1.50 [1.20; 1.88]	0.0004			1.77 [1.39; 2.26]	<0.0001	1.40 [1.05; 1.88]	0.0234
Plaques (yes vs. no)	1.16 [0.55; 2.42]	0.6988			2.64 [1.18; 5.91]	0.0179		
Age (10-year increase)	2.17 [1.52; 3.10]	<0.0001	2.10 [1.46; 3.06]	0.0001	3.20 [1.97; 5.21]	<0.0001	2.19 [1.24; 3.87]	0.0069
Sex (male vs. female)	1.98 [0.98; 3.98]	0.0556			1.96 [0.89; 4.35]	0.0969		
Educational level	0.63 [0.49; 0.81]	0.0003	0.64 [0.49; 0.84]	0.0011	0.75 [0.56; 1]	0.0472		
History of high blood pressure (yes vs. no)	2.69 [0.97; 7.46]	0.0568			0.85 [0.29; 2.53]	0.7723		
History of hypercholesterolemia (yes vs. no)	2.56 [1.25; 5.23]	0.01			2.42 [1.08; 5.42]	0.0310		
History of diabetes (yes vs. no)	1.88 [0.17; 21.23]	0.611			1.41 [0.12; 16.06]	0.7823		
Current or ex-smoker (yes vs. no)	0.91 [0.46; 1.82]	0.7889			0.71 [0.32; 1.56]	0.3951		
SBP, mm Hg	1.01 [0.99; 1.03]	0.4442			1.01 [0.99; 1.04]	0.3783		
DBP, mm Hg	1 [0.97; 1.03]	0.8926			1 [0.96; 1.04]	0.9789		
BMI	1.06 [0.97; 1.17]	0.1974			1 [0.9; 1.12]	0.9474		
HDL, mmol/l	0.61 [0.26; 1.46]	0.2686			0.4 [0.14; 1.13]	0.0841		
LDL, mmol/l	0.92 [0.64; 1.3]	0.6225			0.75 [0.51; 1.12]	0.1581		
Total cholesterol, mmol/l	0.95 [0.72; 1.24]	0.7057			0.79 [0.58; 1.07]	0.1261		
Triglycerides, mmol/l	1.54 [0.85; 2.79]	0.1538			1.35 [0.75; 2.43]	0.3144		
Glycated hemoglobin	1.32 [0.62; 2.8]	0.4765			0.69 [0.28; 1.69]	0.4156		
Blood glucose, mmol/l	0.95 [0.68; 1.33]	0.7687			0.72 [0.5; 1.03]	0.0740		
Homocysteine, μmol/l	1.09 [1; 1.2]	0.0444			1.08 [0.99; 1.18]	0.0958		
CRP, mg/l	1.01 [0.97; 1.06]	0.6327			1.04 [0.99; 1.09]	0.1335		
Fibrinogen, g/l	1.4 [0.85; 2.29]	0.1876			1.97 [1.12; 3.48]	0.0186		

hypercholesterolemia (n = 65, 45.5%), diabetes (n = 3, 2.1%), current or ex-smoking (n = 69, 48.3%).

Vascular Risk Factors and Carotid Atherosclerosis (table 1)

Carotid plaques or stenosis were found in 48 out of 144 patients (33.3%). In univariate analysis, carotid plaques or stenosis were found associated with age, male sex and systolic blood pressure (table 1), in multivariate analysis the association was found significant only with age and male sex.

134 out of 144 patients had cIMT measurement available. The mean cIMT was 0.63 ± 0.1 mm (median 0.61, range 0.47–0.91). cIMT was found associated with age, educational level, and fibrinogen in univariate analysis, only with age and educational level in multivariate analysis (see table 1).

Main Clinical Manifestations and Carotid Atherosclerosis (table 2)

Cognition

Using the median MDRS score of 140 as the cutoff value for the presence of moderate cognitive impairment, we found, in univariate analysis, that age, educational level, cIMT, the presence of plaques, a positive history of hypercholesterolemia and homocysteine level were significantly associated with MDRS <140. In multivariate analysis, only higher age and lower educational level were independently correlated with moderate cognitive impairment (AUC 0.777 [0.968; 0.857], optimism 0.77%).

When using the lower quartile limit of MDRS (127) as the cutoff value for the presence of severe cognitive impairment, while univariate analysis showed a significant association with cIMT, the presence of plaques, age, male sex, educational level, hypercholesterolemia and fibrinogen level, multivariate analysis showed that only higher cIMT and older age were the only factors independently associated with lower cognitive performances (AUC 0.833 [0.761; 0.905], optimism 0.75%).

Disability and Stroke

Thirty-two out of 144 (22.2%) patients were disabled (mRS ≥3). In table 3, the factors associated with mRS ≥3 and stroke in multivariate analysis are presented. When the inclusion of the variable 'age' was forced in the model, we found higher age and lower level of HbA_{1C} independently associated with disability and a trend for an association between higher cIMT and disability.

Table 3. Summary of factors associated with different clinical or MRI markers after multivariate analysis

Clinical and MRI variable tested in the model	Markers with significant association	Regression parameter[1] [95% CI]	p	AUC [95% CI] or R^2, optimism
mRS ≥3 (n = 32/144)	cIMT (0.05-mm increase)	1.31 [0.99; 1.72]	0.0598	0.809 [0.725; 0.894]
	age (10-year increase)	2.10 [1.22; 3.61]	0.0073	2%
	glycated hemoglobin	0.12 [0.03; 0.49]	0.003	
Clinical history of stroke (n = 93/144)	age (10-year increase)	1.56 [1.14; 2.14]	0.0055	0.662 [0.562; 0.763]
	sex (male vs. female)	2.38 [1.15; 4.93]	0.0191	1.3%
WMH	age	0.19 [0.13; 0.25]	<0.0001	21.2%
				1.7%
Total volume of lacunes	age	0.04 [0.02; 0.05]	0.0002	11.9%
	LDL	–0.06 [–0.11; –0.00]	0.0389	2.6%
Mean ADC	presence of carotid plaques or stenosis	1.09 [0.42; 1.76]	0.0018	27.4%
				5.5%
	age	0.04 [0.01; 0.07]	0.0121	
	LDL	–0.57 [–0.94; –0.20]	0.0029	
BPF	age	–0.25 [–0.36; –0.14]	<0.0001	29.2%
	sex	–3.70 [–6.18; –1.22]	0.0039	3.4%
Presence of microhemorrhages	age (10-year increase)	1.84 [1.08; 3.15]	0.0248	0.758 [0.654; 0.862]
	systolic blood pressure	1.03 [1.00; 1.06]	0.0292	1.5%

[1] Regression parameter stands for OR and 95% CI or slope and 95% CI in logistic regression or linear regression, respectively. Only significant results obtained in multivariate analysis are shown.

Ninety-three out of 144 patients had a history of symptomatic stroke. The multivariate analysis revealed only higher age and male sex to be independently associated with stroke in the cohort but not the markers of atherosclerosis (cIMT and plaques).

Brain MRI Markers and Atherosclerosis

The significant associations observed in multivariate analysis are presented in table 3; the extent of white matter lesions in the 144 CADASIL patients was only associated with age but not with the other parameters (table 3).

For the total volume of lacunes, we found a significant association with increasing age and with lower HDL level. The mean ADC was independently associated with the presence of plaques or stenosis, higher age and higher LDL. The same significant association was obtained between peak value of diffusion histograms and both higher LDL and the presence of plaques. The presence of two or more microhemorrhages was associated with increasing age and with higher systolic blood pressure. BPF was inversely correlated with age and was significantly lower in men compared to women.

Discussion

In this large prospective cohort of CADASIL patients, we found that atherosclerosis has an impact, although small, on the clinical phenotype of this genetic non-atherosclerotic vascular disease of the brain. Indeed, in patients with the lowest cognitive performances, cIMT and age were found to be independently and inversely correlated with the MDRS. Interestingly, this association was not detected in patients with moderate cognitive impairment in whom age and education level were the only predictors of cognitive performances. These results first confirm the major role of aging in the course of CADASIL and second suggest that educational level may have a positive impact on cognitive function in CADASIL during its early stages, while atherosclerosis may play a negative role at more advanced stage of the disease when cognitive decline has already occurred. However, the identified link between atherosclerosis and cognitive decline in this cohort of CADASIL patients does not mean necessarily a causal relationship. First, cognitive impairment may magnify vascular risk factors through a reduction of self-care. Second, atherosclerosis and dementia may share

common unknown risk factors including potential genetic factors. Interestingly, cIMT has also been associated with more severe cognitive alterations in cohort studies of Alzheimer's disease [20–22]. Our data suggest that atherosclerosis may also have an impact on the course of non-atherosclerotic small vessel disease of the brain.

In the present study, we were unable to demonstrate any strong association between atherosclerosis and disability assessed by mRS, which is a score more correlated to motor than cognitive impairment. We also failed to show any significant association between atherosclerosis and the occurrence of stroke in CADASIL. It is, however, known that the frequency of stroke is not a major determinant of clinical severity in CADASIL, which at its advanced stages has a more progressive course [15].

Since cognitive impairment is strongly related to brain MRI lesions in CADASIL, we searched for an association between the most important MRI markers of the disease and carotid markers of atherosclerosis. The presence of carotid plaques or stenosis was found to be significantly associated with both the mean and peak values of cerebral diffusion histograms. These findings suggest that atherosclerosis may interact with the severity of microstructural cerebral tissue lesions in CADASIL. In contrast, in multivariate analysis, no significant association was detected between cIMT or carotid plaques or stenosis and the total load of lacunar infarctions, extent of WMH, number of microhemorrhages, or BPF. As expected, age was found to be strongly associated with all studied brain MRI parameters of the disease [2].

This study has several limitations. First, we did not use quantitative data such as the surface or volume of carotid plaques, which may be more specific for the evaluation of the severity of atherosclerosis than the degree of carotid stenosis [23]. Second, we did not consider in the multivariate analysis the impact of the underlying Notch3 mutations nor studied other genotypes like ApoE. However, although ApoE genotype is strongly related to cognitive impairment in the general population, it has not been found to be associated with the clinical severity of CADASIL [5]. In addition, there is no data to support a genotype phenotype correlation in CADASIL [9], except rare mutations within the ligand-binding domain of Notch3 that may influence the phenotype of the disease [7]. Furthermore, when the analyses were performed after exclusion of the 8 patients harboring this mutation in EGFR10-11 in the cohort, the overall results remained unchanged (data not shown). Finally, there are also different biases related to this cohort of a rare disorder that may also preclude to observe stronger effects of atherosclerosis and a significant association between cIMT and the usual vascular risk factors such as the relatively young age of participants, their selection based on the presence of MRI lesions not explained by vascular risk factors, their high education level, active prevention of vascular risk factors and strong medical follow-up.

In conclusion, the results of this study suggest that atherosclerosis may influence, although subtly, the cognitive decline in CADASIL, which may occur through an increase in microstructural cerebral tissue loss. Longitudinal studies in larger population of patients are needed to confirm the impact of atherosclerosis on the phenotype of the disease and to determine whether treating classical vascular risk factors of atherosclerosis may improve the course of the disease.

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