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ORIGINAL RESEARCH

Cerebrovascular Reactivity Is a Main Determinant of White Matter Hyperintensity Progression in CADASIL

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BACKGROUND AND PURPOSE: Basal total cerebral blood flow (TCBF) and cerebrovascular reactivity (CVR) are assumed to play an important role in the pathophysiology of small-vessel disease. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a unique monogenetic model to study the pathophysiology of arterial small-vessel disease. The aim of this study was to investigate the role of TCBF and CVR in the progression of MR imaging abnormalities in CADASIL.

MATERIALS AND METHODS: Basal TCBF was measured in 25 *NOTCH3* mutation carriers and 13 control subjects at baseline. CVR after administration of acetazolamide was measured in 14 NOTCH3 mutation carriers and 9 control subjects. Increase in white matter hyperintensities (WMHs), lacunar infarcts, and microbleeds on MR imaging was measured 7 years later.

RESULTS: Lower CVR at baseline was associated with larger increase of WMHs ($P = .001$) but not with a larger increase of lacunar infarcts or microbleeds. TCBF at baseline was not associated with an increase of MR imaging abnormalities.

CONCLUSIONS: Decreased CVR is a potential predictor of disease progression as indicated by increasing WMHs in CADASIL.

Cerebral hemodynamics are known to be impaired in large- and small-vessel disease. In large-vessel disease, both total cerebral blood flow (TCBF) and cerebrovascular reactivity (CVR) are impaired, and CVR in particular is associated with poor clinical outcome.[1]

Small-vessel disease is characterized by white matter hyperintensities (WMHs) and lacunar infarcts and is one of the leading causes of stroke and dementia. It has been found that in small-vessel disease, TCBF and CVR are inversely associated with WMHs.[2,3] However, a limitation is that these studies are cross-sectional, which hampers conclusions about causality. Moreover, WMHs may not only be attributable to arterial factors but also to other age-related mechanisms, such as periventricular venous collagenosis.[4]

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary, monogenic form of small-vessel disease, caused by mutations in the *NOTCH3* gene. The pathologic changes are specifically located in cerebral arterioles and consist of degeneration of vascular smooth muscle cells and fibrous thickening of vessel walls.[5] WMHs, lacunar infarcts, and microbleeds appear at a much younger age than in people with sporadic small-vessel disease.[6] CADASIL is a unique model to study the pathogenesis of small-vessel disease, as the underlying arteriopathy is established and there are marked MR imaging abnormalities at an early age (ie, when age-related mechanisms are unlikely to play a role).

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Imaging studies have demonstrated that TCBF as well as CVR is decreased in CADASIL.[7,8] It has been suggested that these changes precede the development of WMHs and that flow changes are, thus, a key underlying factor in the pathophysiology of CADASIL.[7] However, to our knowledge, no longitudinal studies have been performed to confirm this concept.

The aim of this longitudinal study was to investigate the role of TCBF and CVR in the progression of MR imaging abnormalities in CADASIL and, in this way, also get more insight into the pathophysiology of sporadic small-vessel disease. Our hypothesis is that lower TCBF and CVR are predictors of faster progression of MR imaging abnormalities in CADASIL.

Materials and Methods

Patients

Participants were drawn from the Dutch cross-sectional CADASIL study, performed in 1999 and 2000,[7] which included 40 symptomatic and asymptomatic *NOTCH3* mutation carriers (MCs) and 22 non-mutation carriers (nonMCs) from 15 unrelated families. All living participants were invited for a follow-up visit. Informed consent was obtained from the participant or family member if the participant was unable to provide informed consent. Exclusion criteria were age younger than 18 years at baseline, inability to provide informed consent at baseline, and any contraindication to MR imaging at baseline or at follow-up. A total of 38 members from 12 unrelated families participated in the follow-up study. Twenty-five were MCs and 13 were nonMCs, the latter serving as control subjects for comparisons of baseline flow characteristics between MCs and nonMCs. MR imaging rating was performed blinded to *NOTCH3* mutation status. The local medical ethics committee approved the study.

The follow-up examinations were performed between November 2006 and September 2007. We took a full medical history of all participants and obtained their medical records from their physicians and general practitioners.

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MR Imaging

A uniform MR imaging protocol was performed on the same 1.5T MR system (Philips Medical Systems, Best, the Netherlands) at baseline and at follow-up. Conventional T1-weighted spin-echo images (section thickness, 6 mm; intersection gap, 0.6 mm; TR, 600 ms; TE, 20 ms; matrix, 256 × 205; and FOV, 220 × 165 mm), dual-echo T2-weighted spin-echo images (section thickness, 3 mm; intersection gap, none; TR, 3000 ms; TE1, 27 ms; TE2, 120 ms; matrix, 256 × 205; FOV, 220 × 220 mm), and fluid-attenuated inversion recovery (FLAIR) images (section thickness, 3 mm; intersection gap, none; TR, 8000 ms; TE, 100 ms; inversion time, 2000 ms; matrix, 256 × 192; FOV, 220 × 176 mm) were obtained. To detect cerebral microbleeds, we performed T2*-weighted gradient echo-planar imaging (EPI) (6.0/0.6 mm; TR, 2598 ms; TE, 48 ms; matrix, 256 × 192; EPI factor, 25). All images were performed in the axial plane parallel to the inferior border of the genu and splenium of the corpus callosum. No significant hardware upgrades (same gradient coils and same send/receive coils) were performed to the MR imaging machine during the follow-up interval. We reloaded and used the original scan protocols as were used in the baseline study.

For volumetric MR imaging measurements of WMHs, we used locally developed semiautomated segmentation software (SNIPER, Software for Neuro-Image Processing in Experimental Research) that combines knowledge-based fuzzy clustering and region-growing techniques.[9] After skull stripping, the brain parenchyma, CSF, and WMHs were segmented. WMHs were defined as white matter areas with increased signal intensity on intermediate, T2-weighted and FLAIR-weighted images. The software computes an additional T2/proton attenuation image to distinguish the lesions from CSF. Volume of WMH was corrected for total brain volume by dividing the individual volume of WMH by total brain volume and was expressed in percentage.

The number of lacunar infarcts and microbleeds was counted on a digital workstation by 1 observer (M.A.v.B.). A second observer (M.K.L.) reviewed the scores, and in case of conflicting scores, agreement was reached with a third observer (J.v.d.G.). All observers were blinded to patient data. Studies were scored in random order. Baseline and follow-up scans were scored at an interval of 4 months. Lacunar infarcts were defined as parenchymal defects not extending to the cortical gray matter, with a signal intensity corresponding to that of CSF on all pulse sequences and a diameter more than 2 mm.[10,11] Areas with a diameter larger than 2 mm, but that were located in the lower third of the corpus striatum of the basal ganglia and had a symmetric distribution along the lenticulostriate arteries, were considered to reflect normal dilated perivascular spaces and were excluded as lacunar infarcts.[11]

Microbleeds were defined as focal areas of signal intensity loss on T2-weighted spin-echo images that increased in size on the T2*-weighted gradient EPI ("blooming effect").[10] In this way, microbleeds were differentiated from areas of signal intensity loss on the basis of vascular flow void. Areas of symmetric hypointensity in the basal ganglia likely to represent calcification or nonhemorrhagic iron deposits, and areas of signal intensity loss associated with other focal intra-axial lesions were disregarded.

TCBF and CVR measurements were only performed at baseline and were not repeated at follow-up. To measure TCBF and CVR, we used a gradient-echo phase-contrast technique before and after administration of intravenous acetazolamide.[7,12] Two localizer MR angiography scans (gradient-echo phase-contrast sequence: TR, 17.5 ms; TE, 6.7 ms; flip angle, 7.5°; section thickness, 60 mm; matrix, 256 × 128; FOV, 250 mm) were placed in the region of the cervical and intracranial parts of the basilar and carotid arteries in the coronal plane and in the sagittal plane. These scans were also used to rule out concomitant large-vessel disease. On the basis of the localizer MR angiography scans, a 2D phase-contrast scan plane was positioned perpendicular to the basilar artery and both internal carotid arteries. The imaging parameters were as follows: TR, 16 ms; TE, 9 ms; flip angle, 7.5°; section thickness, 5 mm; matrix, 256 × 154; FOV, 250 × 188 mm; and velocity sensitivity, 100 cm/s. Cerebral blood flow was measured 10 minutes before the administration of 14 mg/kg of acetazolamide intravenously and was repeated at 5, 10, 15, and 20 minutes after the administration of acetazolamide. Flow measurements were analyzed with the internally developed software package FLOW (Division of Image Processing, Department of Radiology, Leiden University Medical Center).[13] This software package has been validated for use in TCBF measurements.[14] After manually delineating a region of interest around the carotid arteries and basilar artery, the software package FLOW calculates the volume of flow in mL/min, by integrating the flow velocity values within the contour multiplied by the area. The sum of the flow in these 3 vessels is considered to represent TCBF. Cerebrovascular reactivity was defined as (maximum TCBF after acetazolamide – baseline TCBF)/baseline TCBF × 100%. Administration of acetazolamide was only performed in people who gave separate informed consent.

Statistics

We performed statistical analysis using the SPSS-14 statistical software package (SPSS, Chicago, Ill). Demographics, flow measurements, and MR imaging abnormalities were compared between MCs and nonMCs with the Student t test, the χ^2 test, and the Mann-Whitney-U test. MR imaging abnormalities were compared between baseline and follow-up with paired Wilcoxon tests. Scatterplots were inspected for possible associations between baseline flow characteristics and progression of MR imaging abnormalities. Because most associations in these plots were found to be nonlinear and because linearity could not be achieved with exponential or logarithmic transformation, we chose to stratify the data instead of using correlation testing. Because of the small sample size in this study, we chose to stratify the MCs into 2 groups of lower and higher TCBF and CVR, rather than the more commonly used stratification into tertiles or quartiles. To produce 2 groups of equal size, we used the median values of TCBF and CVR in MCs as cutoff points. The resulting cutoff points for TCBF were less than 584 mL/min for low TCBF (mean, 485 mL/min; SD, 75 mL/min) and 584 mL/min or more for high TCBF (mean, 683 mL/min; SD, 86 mL/min). The resulting cutoff points for CVR were less than 65% for low CVR (mean, 53%; SD, 10%) and more than 65% for high CVR (mean, 81%; SD, 17%). In addition, we analyzed possible associations between TCBF, CVR, and progression of WMHS using the Spearman rank correlation coefficient. We then compared progression of MR imaging abnormalities between baseline and follow-up between the 2 groups using the Student t test for WMHs and using the Fisher Exact test for lacunar infarcts and microbleeds on the basis of the occurrence of new lacunar infarcts and microbleeds. Significant findings were additionally analyzed with the use of analysis of covariance (ANCOVA) to correct for age and blood flow.

Results

From the 62 original participants, 7 died during the follow-up period. From the 55 that were still alive, 38 participated in the

Table 1: Demographics, flow, and MR imaging characteristics of the study population

	MC (n = 25)		NonMC (n = 13)	
	Baseline	Follow-up	Baseline	Follow-up
Demographics				
Male/female	11/14	11/14	7/6	7/6
Age (SD), years	42.2 (10)	49.4 (10)	36.7 (8)	43.8 (8)
Flow parameters				
TCBF in mL/min (SD)	588 (128)†	–	750 (179)	–
Cerebrovascular reactivity in % (SD)	67 (20)	–	68 (23)	–
MR imaging parameters				
WMH volume in % (SD)	5.0 (3.9)†	7.4 (5.3)**	0.0	0.0
Infarct count (range)	6.2 (0–27)†	9.9 (0–38)**	0	0
Microbleed count (range)	1.6 (0–35)	3.2 (0–40)*	0	0

Note:—MC indicates mutation carriers; NonMC, nonmutation carriers; TCBF, total cerebral blood flow; WMH, white matter hyperintensities. The 2-sample t test is used for comparisons of age, TCBF, and CVR. The Mann-Whitney U test is used for baseline comparisons of WMH volume, infarcts, and microbleeds. The χ^2 test is used for male/female. CVR data are based on measurements in 14 MCs and 9 nonMCs.
* Difference ($P < .05$) between baseline and follow-up.
** Difference ($P < .01$) between baseline and follow-up.
† Difference ($P < .01$) between MCs and nonMCs at baseline.

Table 2: Associations between baseline flow characteristics and progression of MR imaging abnormalities

	Lower TCBF (< 584 mL/min) (n = 12) Mean: 485 SD: 75	Higher TCBF (≥ 584 mL/min) (n = 13) Mean: 683 SD: 86	Lower CVR (< 65%) (n = 7) Mean: 53% SD: 10%	Higher CVR (> 65%) (n = 7) Mean: 81% SD: 17%
Δ WMHs in % (SD)	2.8 (2.7)	2.0 (1.6)	2.9 (1.5)	0.37 (0.03)***
% Subjects with new infarcts	9/12 (75%)	9/13 (69%)	6/7 (86%)	3/7 (43%)
% Subjects with new microbleeds	4/12 (33%)	3/13 (23%)	2/7 (29%)	1/7 (14%)

Note:—CVR indicates cerebrovascular reactivity. The Student t test is used for WMHs; the Fisher Exact test, infarcts and microbleeds.
*** Difference ($P < .001$) between higher and lower.

follow-up study. Reasons for not participating were severe disease,[3] disease-related immobility,[2] hospital anxiety,[2] or lack of interest or motivation.[8] Two individuals did not provide a reason for nonparticipation.

From the 38 participants in the follow-up study, 25 were *NOTCH3* MCs. The average time between baseline and follow-up examinations was 7.1 years (range, 6.4–7.7 years). Eight of the MCs were asymptomatic at the baseline visit. The disease duration in the other MCs ranged from less than 5 years (5 MCs) to 5 to 10 years (5 MCs) and 10 to 21 years (7 MCs). Fourteen MCs and 9 nonMCs gave consent for acetazolamide administration.

There were no significant differences in age and sex distribution between MCs and nonMCs (Table 1). MCs had significantly lower TCBF values than nonMCs ($P = .003$). Mean CVR was not significantly different between the 2 groups. None of the MCs and nonMCs showed any signs of large-vessel disease. The MR imaging characteristics of the MCs and nonMCs at baseline and at follow-up are also shown in Table 1. In MCs, the amount of lacunar infarcts ($P < .01$), WMHs ($P < .01$), and microbleeds ($P < .05$) increased significantly between baseline and follow-up. NonMCs had no lacunar infarcts, microbleeds, or significant (Scheltens score[15] > 1) WMHs at baseline or at follow-up.

Table 2 shows that lower TCBF (< 584 mL/min) was not associated with increase of MR imaging abnormalities. However, patients with lower CVR values at baseline (< 65%) had a significantly larger increase in WMH volume than patients with higher CVR values (uncorrected: $P < .001$, ANCOVA corrected for age and basal TCBF: $P = .016$). Correlation testing confirmed that TCBF was not associated with progression of WMHs, whereas lower CVR was associated with faster progression of WMHs ($P = .01$). This association between CVR and progression of WMHs is also shown in Fig 1. CVR was not associated with an increase in either lacunar infarcts or microbleeds.

Discussion

This study shows that lower CVR at baseline in CADASIL patients is associated with a larger increase of WMHs at follow-up but not with a larger increase in lacunar infarcts or microbleeds. We found no effect of TCBF at baseline on progression of any of these radiologic markers of small-vessel disease.

This study is the first to establish an important role for CVR on longitudinal progression of WMHs in CADASIL. This finding supports the hypothesis that decreased CVR is an important factor in the pathophysiology of small-vessel disease.

The finding that only CVR and not TCBF, though decreased in CADASIL, had prognostic value on the development of WMHs suggests that factors other than hypoperfusion per se play a role in the pathogenesis of WMHs, or that threshold levels of hypoperfusion below which WMH develop are only reached when CVR is impaired. It is possible that other factors play a role, such as the nocturnal blood pressure dips that have been reported in CADASIL patients.[16,17] During these dips, the impaired CVR may fail to sufficiently regulate normal cerebral perfusion.

Progression of lacunar infarcts and microbleeds was not associated with TCBF or CVR. It is possible that these have a different pathophysiology. However, a lack of significant association could also be caused by the small sample size of this study. Another factor that may have influenced these associa-

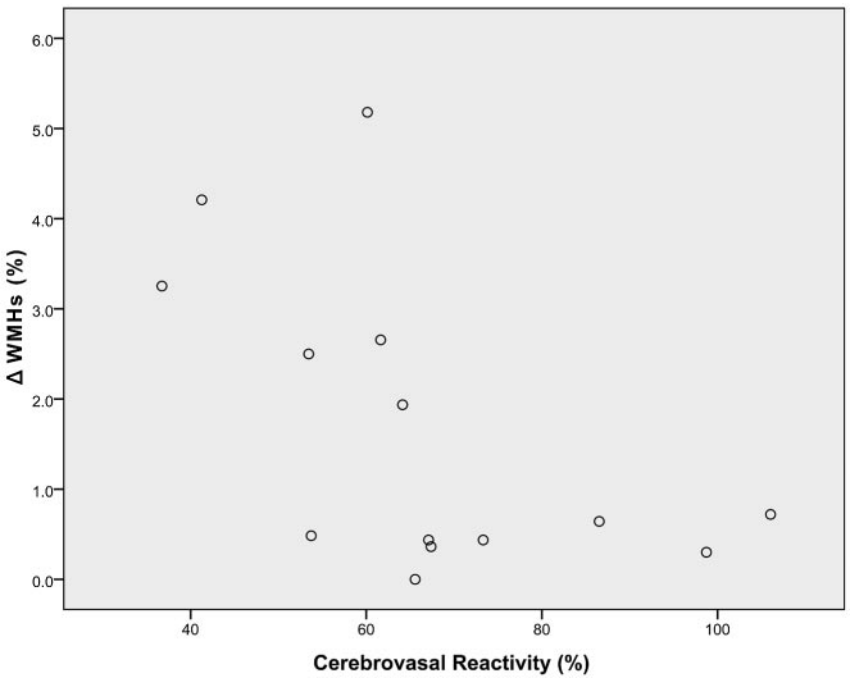

Fig 1. Association between baseline CVR and progression of white matter hyperintensities in MCs.

tions is the limited ability of MR imaging to distinguish small lacunar infarcts from small, infarctlike white matter lesions.

A possible clinical application of these results could be the use of CVR as a predictive test of disease progression in patients with CADASIL. However, to determine the predictive accuracy of this test at different cutoff points in individual patients, a larger sample size is needed.

A limitation of this study was the small sample size and the loss to patient follow-up. Also some CVR measurements were missing because not all people participated in the study part with administration of acetazolamide. This may have resulted in a selection of relatively healthy participants at baseline. However, this selection also has its advantages because patients with a relatively early disease stage of CADASIL may clinically and radiologically more closely resemble the general population with small-vessel disease. Another limitation was the relatively arbitrary division of the data into low and high TCBF and CVR that we performed because of the small sample size. Some subjects had CVR values that were close to the dividing line of 65% but had very different rates of WMH progression.

Conclusions

This study shows that lower CVR is an important determinant of development of WMHs in CADASIL. Because CADASIL is good model for sporadic small-vessel disease, longitudinal studies in selected populations at risk are warranted to investigate the role of CVR in the pathophysiology of sporadic small-vessel disease

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