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Dilated Perivascular Spaces in Small-Vessel Disease: A Study in CADASIL

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Key Words
Dilated perivascular space · Small vessel disease · CADASIL · Magnetic resonance imaging · Risk factors · Cognition

Abstract
Background and Aim: Dilated perivascular spaces (dPVS) have previously been associated with aging and hypertension-related cerebral microangiopathy. However, their risk factors, radiological features and clinical relevance have been poorly evaluated in CADASIL (cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy), a unique model to investigate the pathophysiology of ischemic small-vessel disease. The purpose of this study was to investigate these different aspects in a large cohort of patients with this disorder. ***Methods:*** Demographic and MRI data of 344 patients from a prospective cohort study were analyzed. The severity of dPVS was evaluated separately in the anterior temporal lobes, subinsular areas, basal ganglia and white matter, using validated semiquantitative scales. Logistic and multiple linear regression models were used to determine the risk factors associated with the severity of dPVS in these different regions and their relationships with cognition, disability and the MRI markers of the disease (white matter hyperintensities (WMH) lacunar infarcts, microbleeds and brain parenchymal fraction (BPF)). ***Results:*** The severity of dPVS was found to increase with age regardless of cerebral area ($p < 0.001$). In contrast with dPVS in other locations, the severity of dPVS in the temporal lobes or subinsular areas was also found strongly and specifically related to the extent of WMH ($p < 0.001$). Conversely, no significant association was detected with lacunar volume, number of microbleeds or BPF. A high degree of dPVS in the white matter was associated with lower cognitive performances independently of age and other MRI markers of the disease including BPF ($p \leq 0.04$). ***Conclusions:*** In CADASIL, the progression of the hereditary microangiopathy with aging may promote the dilation of perivascular spaces throughout the whole brain but with variable extent according to cerebral location. In temporal lobes and subinsular areas, dPVS are common MRI features and may share a similar pathogenesis with the extension of WMH during the course of the disease. dPVS may also participate in the development of cognitive decline in this model of small-vessel disease, and their large number in white matter may alert clinicians to a higher risk of cognitive decline in CADASIL.

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Introduction

The severity of dilated perivascular spaces (dPVS) seen on MRI was previously found related to aging, hypertension, cognitive decline and dementia in elderly subjects [1–3]. It is now considered as an important marker of cerebral small-vessel disease (SVD) due to its strong and independent association with white-matter hyperintensities (WMH) and lacunar infarcts [1, 4, 5]. There is increasing evidence that the topography of dPVS is related to different pathophysiological mechanisms. Compared to dPVS in white matter, dPVS in basal ganglia appear more strongly linked to hypertension [1, 4–6]. By contrast, dPVS in white matter have been independently related to incident dementia in the healthy elderly [3] or to a higher load of lobar microbleed which is strongly suggestive of cerebral amyloid angiopathy [7]. Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most frequent hereditary ischemic SVD, responsible for transient ischemic attacks, stroke, mood disturbances, gait difficulties, cognitive decline and dementia as observed in SVD related to hypertension and aging [8, 9]. Although previous findings showed that CADASIL patients can also present with a high frequency of dPVS especially in temporal lobes or basal ganglia [10], whether the topography of dPVS in this disease corresponds with different risk factors and MRI markers remains poorly understood. Cumurciuc et al. [10] failed to find any significant association between dPVS and other MRI markers of this disease in a small sample. Herein, we investigated the severity of dPVS according to their location, their association with other MRI markers of the disease and their potential clinical significance in a large cohort of CADASIL patients.

Materials and Methods

Subjects

A total of 379 patients from a prospective cohort study were enrolled at Lariboisière (Paris) or at Ludwig-Maximilians-Universität (Munich) hospitals. All cases were confirmed by identification of a typical mutation in the Notch3 gene [8]. The complete study design has been detailed elsewhere [11]. All patients gave their written consent. An independent ethics committee in both centers approved the study.

Magnetic Resonance Imaging

MRI scans were performed using a 1.5-tesla system. Three-dimensional (3-D) T1-weighted axial sequences, fluid-attenuated inversion recovery (FLAIR), T2*-weighted gradient echo planar imaging and proton density images were used for analysis as previously described [12]. MRI data from both centers were collected and processed at BioClinica (Lyon, France) and analyzed together by trained neurologists or neuroradiologists blinded to the clinical data.

Image Processing and Analysis

Analysis of dPVS

The evaluation of dPVS was performed using 3-D T1-weighted images in association with T2-weighted and FLAIR images. dPVS were defined as CSF-like signal intensity (hypointense on T1 and hyperintense on T2) lesions that were round, ovoid or linear, <3 mm in their maximum diameter, with smooth delineated contours and located in areas supplied by perforating arteries. For each lesion fulfilling these criteria except for their diameter ≥3 mm, further efforts were obtained to differentiate them from infarcts by using multiplanar reformatting. Only signal changes with a typical vascular shape and following the orientation of perforating vessels (including cystic lesions having an extension of vascular shape) were then regarded as dPVS [1].

In each subject, dPVS were firstly scored in 'specific' areas, i.e. in the white matter underlying the cortex (superior, middle or inferior temporal gyri) of the anterior pole of temporal lobes (temporal dPVS) and underlying the whole insular cortex (subinsular dPVS). In each area, dPVS were assessed bilaterally, and the score was based on the highest number of dPVS measured in the corresponding region in one slice. Temporal dPVS (fig. 1a) or subinsular dPVS (fig. 1b) were recorded using a 4-grade scale as follows: degree 1 when their number was <5; degree 2 when their number was between 5 and 10; degree 3 when it was between 10 and 20 or when they were detected as a continuous line underlying less than 1 temporal cortical gyrus or half of the insular cortex; degree 4 when their number was >20 or in the presence of a continuous line underlying more than 1 temporal cortical gyrus or half of the insular cortex. Finally, dPVS was evaluated in the global white matter after excluding the previous regions and in basal ganglia (caudate, putamen, pallidum) as already done in a previous study using 4-grade scales (fig. 1c and d, respectively) [1].

All images were analyzed by the same experienced reader (M.Y.) blinded to the clinical data. When the reader was uncertain (n = 45 cases), the lesions were reviewed by another reader with a long experience in MRI studies (H.C.) and a decision was made by consensus. The intrarater agreement for the rating of dPVS was assessed on a random sample of 38 subjects at 1-month intervals. The intrarater reliability analysis showed a good reliability with kappa values of 0.76, 0.81, 0.79 and 0.75 for temporal, subinsular, basal ganglia and white-matter dPVS, respectively.

Analysis of the other MRI Markers of the Disease

Lesions were defined according to the standards for reporting vascular contributions to neurodegeneration [13], and their quantification was made as previously described [11]. Briefly, WMH were analyzed on all axial FLAIR slices from the base of the cerebellum to the vertex (without including hyperintensities in the deep gray matter). Lacunar infarcts were assessed on 3-D T1-weighted scans as round or ovoid hypointense lesions with signal intensity identical to that of CSF and of a diameter between 3 and 5 mm, clearly distinct from dPVS. Determination of global brain volume from 3-D T1-weighted MRI was made as previously described using the Brainvisa software (http://brainvisa.info) [12]. The volume of the total intracranial cavity (ICC) was calculated as the sum of the total volume of cerebral parenchyma and that of cerebral spinal fluid. Brain parenchymal fraction (BPF) was defined as the ratio of brain tissue volume to ICC vol-

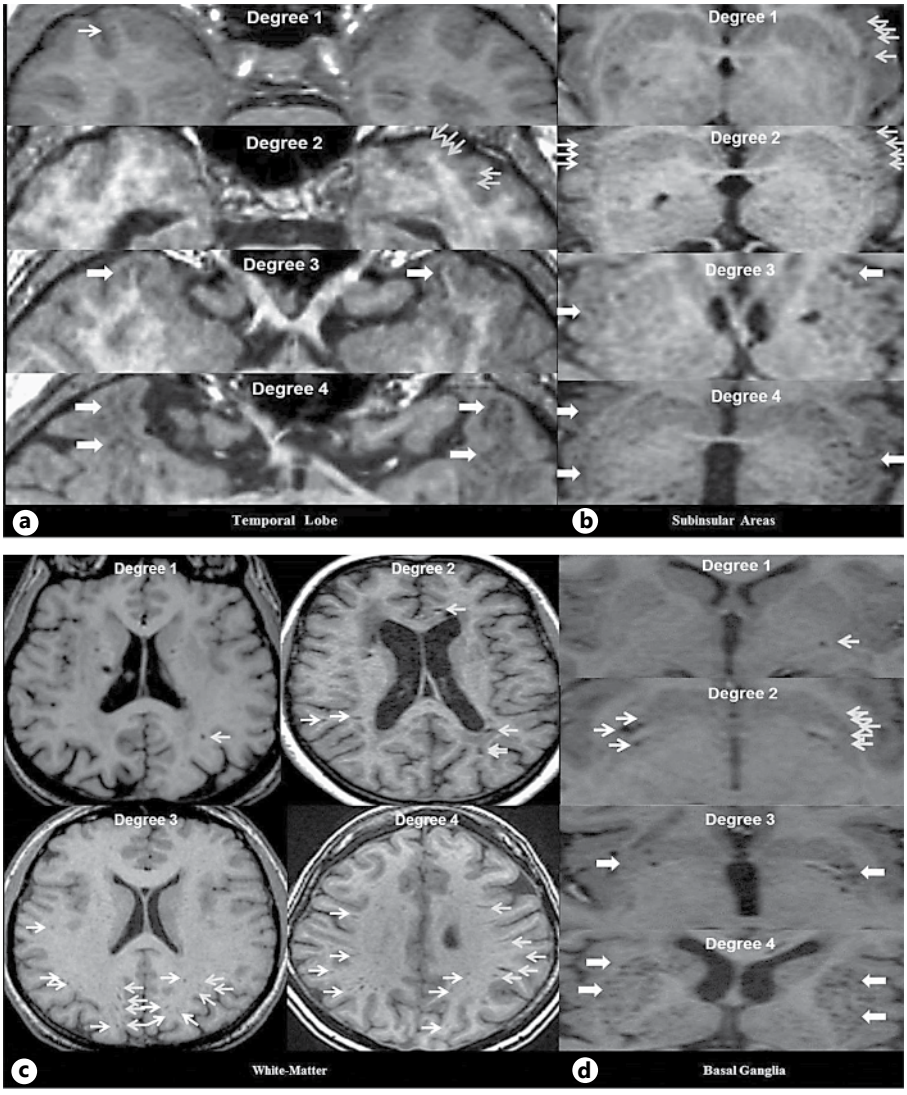

Fig. 1. Examples of severity of dPVS in temporal lobes (**a**), subinsular areas (**b**), white matter (**c**) and in basal ganglia (**d**).

ume. The number of cerebral microbleeds, defined as rounded hypointense foci ≤5 mm in diameter on the gradient echo sequence distinct from vascular flow voids, leptomeningeal hemosiderosis or nonhemorrhagic subcortical mineralization, was also obtained.

Statistical Analysis

In order to have enough power with a relatively large sample, the severity of dPVS was categorized for each patient as dPVS of low severity (degree 1 or 2) or of high severity (degree 3 or 4) in each region. The descriptive analysis was based on this classification. Logistic regression models were computed with dichotomized dPVS load and using the low severity of dPVS as the reference category. Separate analyses were performed in the models used for evaluating the severity of dPVS in different regions: (1) the analysis of risk factors related to the severity of dPVS and their relationships with the other MRI markers of the disease were adjusted for age, gender and ICC; (2) the analysis of correlations with brain atrophy was adjusted for age, gender, number of microbleeds, WMH and lacunar volume.

To evaluate whether the load of dPVS is a risk factor of dementia, another logistic regression model was built with the presence/absence of dementia using the latter as the reference category. Dichotomized dPVS severity, age, gender, educational level and ICC were incorporated as independent variables. Thereafter, to evaluate whether other MRI markers of the disease could modify the association between dementia and degree of dPVS, additional confounders including number of microbleeds, WMH and lacunar volume with/without BPF, were built. Finally, multiple stepwise linear regression analyses (dependent variable = different clinical scores) were performed to assess the relationships between the dPVS severity and different neuropsychological or neurological scores. The same covariates were included as mentioned above. Logarithmic transformations were used when continuous variables were not distributed normally.

Statistical analyses were performed using SPSS version 20.0 for Windows (SPSS Inc.). All p values were two-tailed, and criteria for significance were $p < 0.05$.

Results

Among the 379 patients of the cohort, 344 patients had full sets of MR images of sufficient quality for complete postprocessing measurements. Their demographic, clinical and main MRI features are summarized in table 1. The mean age of patients in the cohort was 50.8 years (SD = 11.6); 43.3% (n = 149) of the subjects were men.

One or more dPVS were detected in each cerebral area in all individuals. Sixty-eight percent of subjects had dPVS of degree 3 or 4 in the temporal lobes, 54.4% in the subinsular area. Conversely, 73.5% of individuals presented dPVS of degree 1 or 2 in basal ganglia and 78.5% in the global white matter (table 1).

dPVS in White Matter or Basal Ganglia

Risk Factors Associated with the Severity of dPVS in White Matter or Basal Ganglia

The potential risk factors related to the severity of dPVS in different cerebral regions are presented in table 2. The severity of dPVS in basal ganglia or white matter was found to increase with age ($p < 0.001$). Men had a higher risk than women of presenting severe dPVS in basal ganglia ($p = 0.047$) but not in white matter. In contrast, severity of dPVS in these two areas was not found related to smoking status, hypertension, hypercholesterolemia, diabetes or history of stroke.

Relationships between the Severity of dPVS in White Matter or Basal Ganglia and the Other MRI Markers of the Disease

After adjustment for age, gender and ICC, no significant association was detected between the severity of dPVS in basal ganglia or white matter and WMH volume or number of microbleeds (table 3). Only the severity of dPVS in basal ganglia was positively related to lacunar volume with a borderline significance ($p = 0.05$).

After adjustment for age, gender, number of microbleeds, WMH and lacunar volume, no significant association was observed between the severity of dPVS in these two areas and BPF.

Relationships between the Severity of dPVS in White Matter or Basal Ganglia and Cognition or Disability

After adjustment for age, gender, educational level and ICC, demented subjects were found to have a higher risk than nondemented patients to present severe dPVS in basal ganglia ($p = 0.02$) and in white matter ($p = 0.04$; table 4). When number of microbleeds, WMH and lacunar volume were incorporated into the model, this association remained significant in basal ganglia ($p = 0.03$) but not in white matter. No significant association was detected when BPF was additionally introduced into the model.

The stepwise multivariate analysis including the same covariates also showed that the white-matter dPVS sever-

Table 1. Main characteristics of patients with CADASIL (n = 344)

Demographic data	
Mean age ± SD, years	50.8±11.6 [23–79]
Male gender, %	43.3
History of stroke, %	63.2
Hypertension, %	25.4
Hypercholesterolemia, %	40.9
Diabetes, %	1.5
Current smoking, %	22.7
Dementia, %	11.1
Disability and cognitive scores	
Mean, median modified Rankin scale	0.95, 0 [0–5]
Mean, median MMSE	26.95, 28 [7–30]
Mean, median MDRS	134.27, 141 [35–144]
MRI markers	
Median absolute volume of WMH, cm^3	82.046 [0–418.412]
Median absolute volume of lacunar infarcts, mm^3	0.359 [0.00–5.181]
Median number of CM[a]	11 [1–141]
Median BPF	86.53 [65.33–96.50]
Temporal dPVS, %	
Degree 1	10.2 (35)
Degree 2	21.8 (75)
Degree 3	53.2 (183)
Degree 4	14.8 (51)
Subinsular dPVS, %	
Degree 1	14.5 (50)
Degree 2	31.1 (107)
Degree 3	42.4 (146)
Degree 4	11.9 (41)
BG dPVS, %	
Degree 1	11.6 (40)
Degree 2	61.9 (213)
Degree 3	24.7 (85)
Degree 4	1.7 (6)
WM dPVS, %	
Degree 1	31.4 (108)
Degree 2	47.1 (162)
Degree 3	19.5 (67)
Degree 4	2.0 (7)

Figures in square brackets indicate ranges, those in parentheses are patient numbers. CM = Cerebral microbleeds; BG = basal ganglia; WM = white matter.

[a] Calculated only in patients with cerebral microbleeds.

Table 2. Crude distribution of potential risk factors across the severity of dPVS and their associations with the severity of dPVS

	Temporal dPVS			Subinsular dPVS			BG dPVS			WM dPVS		
	degrees 1 + 2	degrees 3 + 4	degrees 3 + 4 vs. 1 + 2, p value	degrees 1 + 2	degrees 3 + 4	degrees 3 + 4 vs. 1 + 2, p value	degrees 1 + 2	degrees 3 + 4	degrees 3 + 4 vs. 1 + 2, p value	degrees 1 + 2	degrees 3 + 4	degrees 3 + 4 vs. 1 + 2, p value
Mean age ± SD, years	46.7± 11.8	52.7± 11.0	<0.001 (OR 1.71, 95% CI 1.33–2.18)	45.3± 10.0	55.4± 10.8	<0.001 (OR 2.82, 95% CI 2.13–3.74)	48.6± 11.5	56.9± 9.6	<0.001 (OR 2.23, 95% CI 1.67–2.98)	49.6± 11.2	55.0± 12.0	<0.001 (OR 1.60, 95% CI 1.20–2.14)
Male gender	44.5	42.7	0.64	43.3	43.3	0.50	40.3	51.6	0.047 (OR 2.11, 95% CI 1.01–4.42)	39.6	56.8	0.79
History of stroke	56.7	66.2	0.69	57.7	67.7	0.95	59.4	73.7	0.28	62.5	66.1	0.55
Hypertension	20.4	27.8	0.64	19.5	30.4	0.60	22.4	33.3	0.87	23.5	32.4	0.61
Hypercholesterolemia	26.8	47.1	0.052	29.8	50.0	0.16	37.2	51.4	0.53	39.8	45.3	0.45
Diabetes	1.2	1.6	0.87	1.6	1.4	0.78	2.0	0	NE	1.8	0	NE
Current smoking	22.9	22.7	0.26	31.1	15.9	0.19	25.5	14.7	0.49	26.2	8.0	0.09

All data are presented as percentages unless otherwise indicated. In each logistic regression model, dPVS in different cerebral areas was considered as the dependent variable, ICC volume and age or/and gender as confounding factors. For continuous variables, the odds ratio (OR) estimates the association related to an increase of 1 SD. Only when $p < 0.05$, were odds ratio values listed. BG = Basal ganglia; WM = white matter; CI = confidence interval; NE = not estimated.

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Table 3. Crude distribution of MRI markers across the degree of dPVS and their associations with the severity of dPVS

	Temporal dPVS			Subinsular dPVS			BG dPVS			WM dPVS		
	degrees 1 + 2	degrees 3 + 4	degrees 3 + 4 vs. 1 + 2, p value	degrees 1 + 2	degrees 3 + 4	degrees 3 + 4 vs. 1 + 2, p value	degrees 1 + 2	degrees 3 + 4	degrees 3 + 4 vs. 1 + 2, p value	degrees 1 + 2	degrees 3 + 4	degrees 3 + 4 vs. 1 + 2, p value
Absolute WMH volume[a], cm^3	58.72 (46.00)	115.59 (71.60)	<0.001 (OR 3.51, 95% CI 2.28–5.40)	65.26 (51.86)	124.48 (71.43)	<0.001 (OR 2.42, 95% CI 1.71–3.43)	90.93 (70.62)	115.48 (64.20)	0.88	91.85 (66.59)	118.16 (77.28)	0.22
Absolute lacunar infarct volume[a], cm^3	0.25 (0.49)	0.029 (0.051)	0.11	0.27 (0.56)	0.43 (0.71)	0.14	0.30 (0.52)	0.53 (0.90)	0.05	0.32 (0.64))	0.49 (0.68)	0.52
Cerebral microbleeds[a]	11 (24)	11 (20)	0.48	6 (11)	12 (23)	0.26	11 (20)	10 (22)	0.69	10 (22)	13 (19)	0.69
BPF[b]	86.72 (5.87)	85.02 (6.52)	0.61	87.43 (4.84)	83.99 (7.04)	0.26	86.56 (6.51)	82.64 (6.51)	0.23	86.28 (5.86)	82.57 (7.45)	0.07

All data are presented as means with standard deviations in parentheses. In each logistic regression model, dichotomized dPVS in different cerebral locations was considered as the dependent variable. For continuous variables, the odds ratio (OR) estimates the association related to an increase of 1 SD. Only when $p < 0.05$, were odds ratio values listed. BG = Basal ganglia; WM = white matter; CI = confidence interval.

[a] Model a: adjustment for age, gender and ICC volume.

[b] Model b: adjustment for age, gender, number of microbleeds, WMH volume and lacunar volume.

Table 4. Associations between severity of dPVS and dementia, cognitive performances and disability

		Dementia		MDRS		MMSE		mRS	
		OR	p	β	p	β	p	β	p
Temporal dPVS									
Degrees 1 + 2		ref.		ref.		ref.		ref.	
Degrees 3 + 4	Model 1	0.98 (0.31–3.07)	0.97	0.009	0.88	–0.004	0.95	0.052	0.37
	Model 2	0.58 (0.16–2.13)	0.41	0.017	0.78	0.011	0.86	0.021	0.70
	Model 3	0.29 (0.06–1.30)	0.10	–0.003	0.96	–0.036	0.53	–0.008	0.89
Subinsular dPVS									
Degrees 1 + 2		ref.		ref.		ref.		ref.	
Degrees 3 + 4	Model 1	2.39 (0.73–7.90)	0.15	–0.055	0.38	–0.052	0.41	0.047	0.44
	Model 2	2.27 (0.65–7.96)	0.20	–0.044	0.49	–0.033	0.59	0.019	0.74
	Model 3	1.63 (0.35–7.49)	0.53	–0.063	0.26	–0.100	0.09	–0.016	0.78
BG dPVS									
Degrees 1 + 2		ref.		ref.		ref.		ref.	
Degrees 3 + 4	Model 1	2.92 (1.17–7.24)	0.02	–0.101	0.10	–0.073	0.22	0.062	0.29
	Model 2	2.87 (1.10–7.51)	0.03	–0.078	0.20	–0.050	0.40	0.033	0.55
	Model 3	2.21 (0.69–7.12)	0.18	0.018	0.75	–0.024	0.68	–0.034	0.52
WM dPVS									
Degrees 1 + 2		ref.		ref.		ref.		ref.	
Degrees 3 + 4	Model 1	2.69 (1.03–7.01)	0.04	–0.200	0.001	–0.147	0.01	0.123	0.03
	Model 2	2.41 (0.87–6.68)	0.09	–0.179	0.002	–0.135	0.02	0.096	0.07
	Model 3	1.33 (0.42–4.23)	0.63	–0.174	0.001	–0.140	0.01	0.078	0.13

Binary logistic regression models for dementia (dependent variable = presence/absence of dementia) and multiple linear stepwise models for MDRS, MMSE and mRS (dependent variable = different cognitive or neurological scores) were built, respectively. Model 1: adjustment for age, gender, educational level and ICC volume; model 2: model 1 + further adjustment for WMH volume, lacunar volume and number of microbleeds; model 3: adjustment for age, gender, educational level, WMH volume, lacunar volume, number of microbleeds and BPF. In the MDRS and MMSE, lower scores indicate worse performances. In the modified Rankin Scale, higher scores indicate worse performances. OR = Odds ratio; ref. = reference category; BG = basal ganglia; WM = white matter. Figures in parentheses indicate 95% confidence intervals.

ity was negatively related to the Mattis Dementia Rating Scale (MDRS) score (standardized coefficients $\beta = -0.200$, $p = 0.001$) and Mini Mental State Examination (MMSE) score ($\beta = -0.147$, $p = 0.01$) and positively related to the modified Rankin Scale (mRS) score ($\beta = 0.123$, $p = 0.03$). After further adjustment on other MRI markers including BPF, the associations between white-matter dPVS and MDRS ($p < 0.002$) or MMSE ($p < 0.02$) score remained significant, whereas the association with the modified Rankin Scale was no longer significant. Conversely, no significant relationship between the severity of dPVS in basal ganglia and any neuropsychological or neurological performances was detected.

dPVS in Temporal Lobes or Subinsular Areas

Risk Factors Associated with the Severity of Temporal or Subinsular dPVS

A positive association between the severity of temporal or subinsular dPVS and age was observed independently of gender and ICC ($p < 0.001$; table 2). No gender effect was detected for the severity of dPVS in these two regions. The severity of temporal and subinsular dPVS was not found associated with the smoking status, hypercholesterolemia, hypertension, diabetes or history of stroke.

Relationships between the Severity of Temporal or Subinsular dPVS and the Other MRI Markers of the Disease

No significant association was detected between the severity of temporal or subinsular dPVS and lacunar volume, number of microbleeds or BPF (table 3).

After adjustment for age, gender and ICC, the severity of dPVS in both temporal lobes and subinsular area was found to be strongly and positively associated with WMH volume ($p < 0.001$) in the cohort. Further adjustment for lacunar volume and number of microbleeds did not change these results (data not shown).

Relationships between the Severity of Temporal or Subinsular dPVS with Cognition and Disability

After controlling for age, gender, educational level and ICC, no significant relationship was observed between the severity of temporal or subinsular dPVS and dementia (table 4). No significant association was either detected with the MDRS, MMSE and mRS scores. Adding other MRI markers to the model did not alter these results.

Discussion

The present results strongly suggest that risk factors and pathogenesis of dPVS may largely vary throughout the whole brain in CADASIL, as observed in hypertension-related SVD or cerebral amyloid angiopathy [4–7]. In the present cohort, severe dPVS seem to develop earlier in the subcortical white matter of temporal lobes or subinsular areas than in the rest of white matter or in basal ganglia. This is observed while the frequency of dPVS of high severity in white matter was close to that observed in elderly participants of the 3-City Study whose mean age was 21 years older [1]. In basal ganglia, the frequency of severe dPVS was even found to be 2.4 times higher in CADASIL individuals than in elderly subjects [1]. Since both scales and MRI sequences were similar in these different studies, this discrepancy appears unlikely related to technical variations but rather suggests that the genetic disease may actually promote dilation of perivascular spaces throughout the whole brain but with a variable amplitude according to cerebral location.

Age was also found to be a risk factor of development of dPVS in our patients in line with previous reports in CADASIL [10] or in individuals with lacunar infacts [4, 5]. This suggests that either aging-related processes, vascular wall alterations during the progression of the disease over decades or both of them may promote the development of dPVS in the present population. Of note, after additional adjustment on microbleeds, WMH and lacunar infarcts, the relationships between the severity of dPVS and age were still significant except in temporal lobes (data not shown). These findings and the rare presence of dPVS in temporal lobes of healthy elderly subjects further suggest that although aging-related processes participate in the pathogenesis of dPVS, the progressive microvascular modification owing to the disease has a different and possibly larger contribution in the development of dPVS in temporal lobes.

The higher prevalence of severe dPVS in basal ganglia detected in men with CADASIL is in line with the gender effect previously reported for dPVS at this location in elderly individuals [1]. In addition, in this area, the severity of dPVS was found to increase with diastolic blood pressure (data not shown), although no global association was detected with hypertension as previously reported in elderly subjects or in patients with lacunar infarcts [1, 4, 5]. This might be explained by the relative low frequency of patients with hypertension in this cohort. Additional analysis in the present study revealed that this gender effect in basal ganglia was no longer significant after further adjustment for diastolic blood pressure or lacunar volume which were both higher in men than in women. Therefore, dPVS might be severer in basal ganglia in men because the microvasculature is particularly vulnerable to the blood pressure regimen.

WMH in the anterior temporal lobe and/or the subinsular area are usually considered as specific features of CADASIL [14]. Although the severity of dPVS in temporal lobes or in subinsular areas was found significantly correlated with that in basal ganglia or in white matter, a large number of subjects presented with a discrepancy larger than 2 degrees of severity between these 2 categories of regions (data not shown). Interestingly, in contrast with the results obtained for dPVS in basal ganglia or in white matter, the severity of temporal dPVS was found strongly and positively related to WMH volume. Altogether, these data further indicate that the mechanisms underlying the development of dPVS may largely vary in different cerebral regions in CADASIL. In temporal lobes or within the subinsular white matter, dPVS appear mainly related to the progression of WMH in line with previous pathological findings showing that edema in temporal lobes is closely related to the accumulation of dPVS in the cerebral tissue [15]. Imaging data suggest that WMH may be related to the increase in brain volume in CADASIL [16]. The present results support that the early development of dPVS in these areas and the extension of WMH may actually share some common pathogenesis in CADASIL.

This is the first report showing a significant association independent of age between dPVS in basal ganglia or in white matter and dementia in CADASIL. After adjustment on number of microbleeds, WMH and lacunar volume, a significant association remained for dPVS in basal ganglia, and a similar trend was detected for dPVS in white matter. However, these effects on dementia disappeared when brain atrophy was taken into account. Conversely, the association between the severity of dPVS in white matter and cognitive performances evaluated using

the MMSE or MDRS was still significant after adjustment for all MRI markers including BPF. These results are in line with data obtained in elderly subjects indicating that the severity of dPVS in white matter or basal ganglia is independently related to cognitive decline and significantly associated with an increased risk of dementia [2, 3]. The present findings strongly suggest that dPVS in addition to the ischemic parenchymal lesions may actually account for cognitive decline and participate in the pathogenesis of cognitive decline in CADASIL. The severity of dPVS in white matter of patients with Alzheimer's disease was previously reported to be greater than that in healthy subjects and related to the severity of cortical and leptomeningeal amyloid angiopathy as well as to the amount of amyloid-β within the cortex [17]. Some failure in the drainage of interstitial fluid along the perivascular spaces due to amyloid-β deposit might be involved in the development of dPVS [18]. In CADASIL, major changes of the cerebral vasculature include loss of medial smooth muscle cells, progressive wall thickening, adventitial fibrosis, luminal narrowing and the secondary accumulation of granular osmiophilic material and Notch3 protein [19–21]. Otherwise, abundant diffuse deposition of amyloid-β in the cerebral cortex has been reported in a single CADASIL case [22]. Whether the ultrastructural changes in the microvasculature including the accumulation of granular osmiophilic material can also alter the drainage of the interstitial fluid along the perforating vessels in CADASIL and thus contribute to the pathogenesis of cognitive impairment would need further investigations.

The strengths of this study include the large sample size of data and use of millimetric 3-D T1-weighted acquisitions to obtain reliable identifications of dPVS. The present study also has potential limitations. First, because of the cross-sectional design of this study, the exact clinical significance of our results will need confirmation in prospective studies. Second, our identification of dPVS was performed mainly using T1-weighted imaging not using FLAIR images, therefore the severity of dPVS, especially in white matter, might be underestimated due to extensive hyperintensities in most patients. However, smaller voxel size was found associated with a better visibility of dPVS on MRI [23]. 3-D T1-weighted imaging analysis of 0.8–1.19 mm thickness was used in the present study since FLAIR images were 5 mm thick. Groeschel et al. [23] also found a higher detectability of dPVS on coronal T1-weighted images than on axial T2-, sagittal T2-weighted or axial FLAIR images. Third, very small ischemic cavities in the cerebral tissue might have been misclassified as dPVS and vice versa, despite the use of 3-D MRI analysis and large efforts of 2 different readers in difficult cases. Finally, the use of a semiquantitative evaluation for rating the severity of dPVS can limit our ability to detect small effects or differences.

In conclusion, the present data strongly suggest that in CADASIL, risk factors for the development of dPVS throughout the entire brain vary according to cerebral location. dPVS in both temporal lobes and subinsular areas represent a common radiological feature in this disease, their development appears to share some common mechanisms with the early extension of WMH during the course of the disease. dPVS in other areas are less severe and associated with age, gender and vascular risk factors as already reported in healthy elderly subjects but at a higher degree of severity. The development of dPVS, particularly in white matter, may also be associated with mechanisms of cognitive decline independent of the accumulation of ischemic lesions in SVD. Detection of a high degree of dPVS in basal ganglia or white matter in subjects with CADASIL may alert clinicians to their higher risk of cognitive decline.

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Disclosure Statement

None.

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