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Impact of MRI markers in subcortical vascular dementia: A multi-modal analysis in CADASIL

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Abstract

CADASIL is an arteriopathy caused by mutations of the *Notch3* gene. White matter hyperintensities (WMH), lacunar lesions (LL), cerebral microhemorrhages (CM), brain atrophy and tissue microstructural changes are detected on MRI. Using an integrated multi-modal approach, we examined the relative impact of lesion burden and location of these MRI markers on cognitive impairment and disability. Multi-modal imaging was performed on 147 patients from a two-center cohort study. Volume of LL, WMH and number of CM was determined. Whole brain mean apparent diffusion coefficient (mean-ADC) and brain parenchymal fraction (BPF) were measured. In multivariate models accounting for lesion burden and location, volume of LL, mean-ADC, and BPF each had an independent influence on global cognitive function and disability. BPF explained the largest portion of the variation in cognitive and disability scores (35–38%). Brain atrophy has the strongest independent influence on clinical impairment in CADASIL when all MRI markers in the disease are considered together. The results suggest that the clinical impact of cerebral tissue loss plays a principal role in this genetic model of subcortical ischemic vascular dementia.

Keywords

CADASIL; Cerebral microhemorrhage; Lacunar infarction; Atrophy; White matter damage; Cognitive impairment; Disability

1. Introduction

In recent years, a growing body of literature has highlighted the important contribution of cerebrovascular disease to cognitive impairment (Elias et al., 2004). There is considerable evidence to suggest that different measurable cerebral MRI lesions related to small-vessel diseases play an important role in cognitive impairment and disability (Honig et al., 2003; Ivan et al., 2004; Vermeer et al., 2003; Viswanathan et al., 2006b, 2007).

The extent of white matter hyperintensities (WMH) has been linked both to cognitive impairment and disability in different populations with cerebral small-vessel disease (de Groot et al., 2000; Longstreth et al., 1996; Smith et al., 2004; Yoshita et al., 2006). Small, clinically silent brain infarctions identified on baseline magnetic resonance imaging (MRI) scan carry an increased risk for subsequent dementia (Vermeer et al., 2003). Cerebral microhemorrhages (CM) have been associated with executive dysfunction in patients presenting with stroke or TIA (Werring et al., 2004). Microstructural changes on diffusion imaging appear strongly associated with motor and cognitive impairment in various groups (Holtmannspotter et al., 2005; Jouvent et al., 2007; O'Sullivan et al., 2004). Brain atrophy has been strongly associated with cognitive impairment and disability in Alzheimer's disease, in healthy elderly individuals, and in vascular dementia (Fein et al., 2000; Jouvent et al., 2007; Mungas et al., 2005; Peters et al., 2006; Seshadri et al., 2004).

Furthermore, previous work has suggested a differential effect of the location of ischemic or hemorrhagic lesions on cognitive performance or disability (Jokinen et al., 2005; Werring et al., 2004; Yoshita et al., 2006; Zekry et al., 2003). However, the relative importance of each of these factors in small-vessel disease related cognitive impairment is unknown.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a non-atherosclerotic arteriopathy (Joutel et al., 1996) and is considered a model of "pure vascular dementia" (Chabriat and Bousser, 2003). The disease occurs in mid-adulthood and is caused by mutations of the *Notch3* gene on chromosome 19 (Joutel et al., 1996). The main manifestations of the disease include attacks of migraine with aura, mood disturbances, recurrent ischemic strokes, and progressive cognitive decline (Chabriat et al., 1995). Pathologically, there is deposition of electron-dense osmiophilic granular material within the media of small arteries and capillaries (Tournier-Lasserre et al., 1993) in close association with degenerating smooth muscle cells (Ruchoux et al., 1995). These microangiopathic changes are thought to be responsible for vessel wall dysfunction with decreased basal perfusion and hemodynamic reserve leading to extensive subcortical ischemic lesions (Chabriat et al., 2000).

All of the above-described measurable MRI markers, representing different consequences of the underlying microangiopathy, can be seen in CADASIL. Extensive WMH are seen on T2-weighted images (Chabriat et al., 1998) LL on T1-weighted images (Chabriat et al., 1998; Joutel et al., 1996; O'Sullivan et al., 2003), CM on T2*-weighted or gradientecho (GE) images (Dichgans et al., 2002; Viswanathan et al., 2006b, 2007), brain atrophy on quantitative T1 images (Jouvent et al., 2007; Peters et al., 2006), and tissue microstructural changes on diffusion imaging (Chabriat et al., 1999; Holtmannspotter et al., 2005; Jouvent et al., 2007).

The precise relationship of lesion burden and location among the whole spectrum of MRI markers has not been fully investigated. Therefore, in the current study, using an integrated multi-modal model, we sought to determine the impact of global lesion burden, lesion location and clinical factors on cognitive function and disability in CADASIL patients enrolled in a two-center cohort study.

2. Subjects and methods

2.1. Subjects

Subjects were drawn from a two-center prospective cohort study of patients with CADASIL between October 2003 and July 2005. Complete study design is detailed elsewhere (Viswanathan et al., 2006b, 2007). Briefly, in genetically confirmed CADASIL patients, clinical and demographic data were collected. All enrolled subjects underwent detailed baseline neurological examination, including evaluation of cognitive deficits with the mini-mental state examination (MMSE) and Mattis dementia rating scale (MDRS). The Initiation-Perseveration subscale of the MDRS (Mattis-initiation) was used as a marker of executive dysfunction as in previous studies (Mungas et al., 2001). Nine patients did not undergo cognitive testing and were excluded from the analysis. Dementia status was ascribed according to DSM-IV criteria. Disability was measured by modified Rankin scale (mRS) and Barthel index. The mRS ranges from 0 to 6 and is used to assess global functional outcome in subjects with vascular disease. The Barthel index ranges from 0 to 100 and is a widely used measure of functional independence. Patients who were pregnant or had other contraindications to MRI were excluded (2 patients). This left 147 subjects who were included in the analysis.

Informed consent was obtained from each subject or from a close relative if the subject was too severely disabled to give written consent. This study was approved by an independent ethics committee in both participating centers.

2.2. MRI and image analysis

MRI scans were obtained by the use of a 1.5-T system (Vision, Siemens (Munich) or Signa General Electric Medical Systems (Paris)) (Jouvent et al., 2007; Viswanathan et al., 2006b, 2007). 3D T1-weighted sequences, fluid-attenuated inversion recovery (FLAIR), and T2*-weighted gradient-echo planar and diffusion weighted imaging were performed. MRIs from both centers were processed and analyzed together (Bio-Imaging Technologies SAS, Lyon, France). Lesion analysis was performed using established techniques described below (Jouvent et al., 2007; Viswanathan et al., 2006b, 2007).

2.3. WMH quantification

White matter lesions were analyzed on FLAIR images. A mask of lesions was generated from FLAIR images after application of the intracranial cavity (ICC) mask by applying a threshold on signal intensity derived from the signal intensities histogram. The total volume of WMH was normalized to the intracranial cavity in each patient (normalized volume of WMH or nWMH = (volume of WMH/volume ICC) $\times$ 100). High interrater reliability has been demonstrated (intraclass correlation coefficient = 0.998) (Viswanathan et al., 2006b).

2.4. Lacunar volume

Lacunar lesion volume was quantitated on T1-weighted images. Hypointense lesions with a signal identical to that of cerebrospinal fluid (CSF) 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) $\times$ 1000). Good interrater reliability has

been demonstrated for both the volume and number of lacunes (intraclass correlation coefficient = 0.830 and 0.824) (Viswanathan et al., 2006b).

2.5. Microhemorrhages

Microhemorrhages were defined as rounded foci ≤ 5 mm in diameter hypointense on gradient-echo sequences distinct from vascular flow voids, leptomeningeal hemosiderosis, or nonhemorrhagic subcortical mineralization. The location and number of microhemorrhages were recorded. High interrater reliability for the number of CM has been shown (intraclass correlation coefficient = 0.964) (Viswanathan et al., 2006b).

2.6. Determination of mean-ADC

DWI scans were acquired in the X, Y, and Z directions and then averaged to make ADC measurements largely independent of the effects of anisotropic diffusion. Histograms of ADC values from ADC maps were generated for each patient using a bin width equal to $0.1 \times 10^{-4} \text{ mm}^2 \text{ s}^{-1}$ using software developed for this purpose (Bio-Imaging Technologies SAS, Lyon, France). Voxels containing CSF were excluded in all patients before calculation using a superior threshold value at $27 \times 10^{-4} \text{ mm}^2 \text{ s}^{-1}$. To correct for cross subject differences in brain volume each histogram was normalized to the total number of brain tissue voxels. Only the mean-ADC derived from each histogram was used for analysis.

2.7. Brain volume assessment

Determination of global brain volumes from 3D T1 sequences was performed using Brainvisa software (CEA, Orsay, France, <http://brainvisa.info>) (Jouvent et al., 2007). The first step consisted in a field inhomogeneity bias correction (Jouvent et al., 2007). Extraction of non-brain tissue and segmentation of images into grey matter, white matter and cerebral spinal fluid (CSF) were done using a validated histogram analysis algorithm (Jouvent et al., 2007). Additional manual correction was performed after visual inspection. We have shown high intrarater and interrater reliability for determination of brain volume (interclass correlation coefficients 0.945 and 0.922, respectively) (Jouvent et al., 2007). Brain parenchymal fraction was defined as the ratio of brain tissue volume to total intracranial cavity volume ($\text{BPF} = \text{Brain tissue volume}/\text{ICC}$).

2.8. Lesion localization

Lacunar lesions, WMH and CM were localized by two independent and experienced raters. Lesions in the following cerebral areas were recorded: frontal, temporal, parietal, occipital lobes, caudate, thalamus, lentiform nucleus, corpus callosum (anterior, medial and posterior parts), internal capsule (anterior and posterior limbs), cerebellum or brainstem. Lesions were also characterized as being strategic (S) or non-strategic (NS) based on previous literature (Leys et al., 1999; Roman, 2003) in the following way: frontal (S), temporal (NS), parietal (NS), occipital (NS) lobes, frontal (S), temporal (NS), parietal (NS) and occipital (NS) white matter areas, caudate (S), thalamus (S), lentiform nucleus (NS), corpus callosum (anterior part) (S), corpus callosum (medial and posterior parts) (NS), internal capsule anterior limb (including the genu) (S), internal capsule posterior limb (NS), cerebellum (NS) or brainstem (NS).

2.9. Statistical methods

For univariate analysis, chi-square tests were used to compare two categorical variables and analyses of variance were performed to compare continuous variables distributions across groups. Log-transformations were used when continuous variables were not distributed normally but as results were unchanged before or after transformation, results are presented using the original variables. For univariate MRI marker comparisons, patients were

categorized as non-functionally impaired mRS <3 ($n = 110$) or functionally impaired mRS >3 ($n = 34$). All p values were two-tailed and criteria for significance was $p < 0.05$.

Multiple linear regression models were used to find correlates of disability (mRS, Barthel indices) and cognitive performances (Mattis global rating scale, MMSE, Mattis-initiation). Independent variables were age, gender, education level, center, and MRI markers (mean-ADC, BPF, nWMH, nLV, and CM number). A stepwise procedure was used to optimize the model fit. For each outcome (dependant variable), the correlates are ordered according to the amount of variance explained and a standardized beta coefficient has been calculated so that they are comparable to each other. Search for potential collinearity was investigated using collinearity diagnostics procedures which did not reveal evidence for such an issue.

In order to investigate whether correlates of cognitive performances differ according to the disease stage, we also performed stratified analyses by the presence of absence of dementia based on DSM-IV criteria. Heterogeneity between the two centers was tested by adding an interaction term in the model for each independent variable. But none of them was significant (results not shown).

The effect of brain lesions location on cognition and disability was first investigated for each region separately and in a second step and secondarily for strategic vs non-strategic location (patients were considered to have a strategic lesion if there were one or more lesion(s) in a strategic area). For that purpose, we performed analysis of covariance adjusting for age and gender.

3. Results

3.1. Baseline characteristics of cohort

Baseline characteristics of the cohort are presented in Table 1. Compared to individuals without dementia ($n = 124$), those subjects who met DSM-IV criteria for dementia ($n = 23$) were older (60.7 vs 50.2 years) and had more severe MRI lesions by all MRI measures. The mean MDRS and MMSE scores were 91.4 and 17.5 in the demented group. Patients with dementia were had significantly lower MDRS scores than those without ($p < 0.0001$).

3.2. Relationship between age and lesion burden

All MRI markers except WMH volume strongly correlated with global cognitive impairment and disability in univariate analysis after adjusting for age and sex (Table 2). However, there were considerable differences in normalized MRI marker burden over the age distribution of patients in the cohort. WMH, LL, and mean-ADC increased while BPF decreased linearly with older age. A linear relationship was not observed with CM. However, CM were more prevalent in older patients ($p = 0.0005$).

3.3. Univariate analysis of the impact of lesion location on cognitive impairment and disability

All patients had WMH localized in the white matter of all lobes. WMH was located in at least one strategic area in all patients. Ninety-one percent of the cohort had lacunar lesions. Sixty-nine percent of patients had lesions in the thalamus, 61% in the brainstem, and 72% in the frontal white matter regions. The majority (89%) had at least one strategically localized lesion. CMs were most commonly located in the thalamus (62%), brainstem (39%), and in the corticosubcortical junction in the temporal areas (37%). Sixty-two percent of patients with CM had at least one strategically located lesion.

After adjustment for age and sex, univariate analysis of individual localization showed MDRS scores to be lower when WMH were present in the anterior part of the corpus callosum (120.4 vs 139.4, $p = 0.0005$) and when CM were present in the caudate (109.3 vs 133.1, $p = 0.0088$) or in the anterior limb of internal capsule (91.0 vs 132.3, $p = 0.0073$). Finally, individuals with caudate CM had lower Mattis-initiation scores after adjusting for age and sex (MDRS-initiation; 23.8 vs 33.1, $p = 0.005$). Similar results were obtained with MMSE as a measure of global cognitive function (data not shown).

No association between specific lesion localizations and disability was seen (data not shown).

More globally for cognitive impairment, only the presence of CM in at least one strategic localization was found to have a significant impact on global cognitive (MDRS) scores. The presence of a lacunar lesions or WMH in at least one of these strategic areas did not have a significant effect (Table 3). The results were similar when MMSE was used as a measure of global cognitive function (data not shown).

3.4. Multivariate analysis of the relative impact of lesion burden and location on cognitive impairment

Stepwise multivariate linear regression using burden and localization of MRI markers and significant clinical variables was performed to determine independent predictors of cognitive impairment. Of the candidate predictors BPF ($\beta = 1.37$ (se = 0.3), $p < 0.0001$), LL ($\beta = -53.8$ (se = 19.1), $p = 0.0057$), and mean-ADC ($\beta = -2.7$ (se = 1.1), $p = 0.012$) were independently associated with worse global cognitive scores as measured by MDRS. Additionally, CM in the caudate were independently associated with lower MDRS scores (103.2 (se = 40.9) vs 134.1 (se = 18.2), $p = 0.0273$). CM in the frontal lobes showed a trend toward lower MDRS scores (106.4 (se = 39.0) vs 133.9 (se = 18.5), $p = 0.0564$). Similar results were seen when MMSE was used (data not shown).

3.5. Multivariate analysis of the relative impact of lesion burden and location on disability

Similarly, multivariate linear regression was performed to determine independent predictors of disability. Of the candidate predictors, only BPF ($\beta = -0.12$ (se = 0.02), $p < 0.0001$), LL ($\beta = 6.19$ (se = 1.2), $p < 0.0001$), and number of CM ($\beta = 0.05$ (se = 0.02), $p = 0.002$) were independent predictors of disability. Localization of lesions did not have a significant impact on disability. Similar effects were seen if either mRS or Barthel index was used as a measure of disability (data not shown).

3.6. Contribution of MRI markers to cognitive impairment and disability

We then performed an analysis to determine the variance explained by each of the significant predictors from the multivariate analyses (Table 4). For global cognitive function, BPF explained 35% of the variance in MDRS scores while LL and mean-ADC together explained an additional 10%. Finally, for disability BPF accounted for 38%, LL 13%, and CM 4% of the variation in mRS scores. The independent influences of BPF, LL, and CM remained when MMSE was adjusted for in the model, although cognitive status accounted for the largest percentage of variation in disability scores (35%, $\beta = -0.13$ (se = 0.02), $p < 0.0001$).

In all of above-described analyses, we found no significant center effect that modified the interpretation of our results.

3.7. Contribution of MRI markers to cognitive impairment and disability in non-demented patients

To test whether the influence of these MRI markers varied by cognitive status, similar multivariable logistic regression and variance analyses were carried to determine independent predictors of cognitive impairment in the subgroup of non-demented CADASIL patients ($n = 124$). In non-demented CADASIL patients, lacunar lesions had the greatest impact on cognition and disability. For global cognitive function, LL explained 20% of the variance in MDRS scores ($\beta = -36.6$ (se = 10.1), $p < 0.0001$) while BPF only explained an additional 7% ($\beta = 0.49$ (se = 0.15) $p = 0.003$). For executive function, LL explained 24% of the variance in MDRS-initiation scores ($\beta = -19.8$ (se = 4.8), $p < 0.0001$), age accounted for 11% ($\beta = -0.10$ (se = 0.04), $p < 0.006$) and BPF accounted for 4% ($\beta = 0.21$ (se = 0.08), $p < 0.01$). Similarly, for disability LL accounted for 24% ($\beta = 5.85$ (se = 1.2), $p < 0.0001$), CM 7% ($\beta = 0.08$ (se = 0.03), $p = 0.003$) and BPF 4% ($\beta = -0.05$ (se = 0.02), $p = 0.007$) of the variation in mRS scores.

4. Discussion

The major finding from this study is that among all MRI markers in the disease, brain atrophy plays the most important role in disability and cognitive impairment in CADASIL, a model of pure subcortical vascular dementia. Secondly, lacunar lesions and tissue microstructural changes exert an independent, but less important influence on disability and cognitive impairment.

Global cognitive function was most strongly associated with BPF (explaining 35% of the observed variance in cognitive scores) and to a lesser degree with LL (7% of observed variance) and mean-ADC (3% of observed variance). Furthermore, BPF explained the majority of variation seen in the Mattis-initiation scores (LL and mean-ADC and age independently accounted for an additional 13%). The Mattis-initiation subscale has been used in previous studies as a marker of executive dysfunction (Mungas et al., 2001). The localization of CM was found to have a small but independent impact on cognitive impairment in the disease.

Similarly, BPF strongly influenced degree of disability (38% of observed variance) with an additional but slight influence of LL. The load of WMH did not have any impact on these clinical scales when all MRI markers were analyzed together.

Although the degree and spectrum of cognitive impairment and its relationship to various MRI markers in CADASIL has been widely described (Buffon et al., 2006; Peters et al., 2005), the relative contribution of each marker to cognitive function has not been examined. Previous work has shown that among the clinical MRI markers in the disease, lacunar lesions exert a strong impact on cognitive status (Viswanathan et al., 2007) which is in line with findings from studies in other populations (Kuller et al., 2005; Mungas et al., 2005; Vermeer et al., 2003). The results from this study demonstrate that when more advanced MRI measures and lesion localization are also considered in these models, brain atrophy has the strongest relative contribution to cognitive impairment in CADASIL.

Among these MRI markers in non-demented patients ($n = 124$), although BPF and LL remained the strongest independent markers of global cognitive function, LL had strongest influence on both executive and global cognitive function. These results may suggest that LL in CADASIL exert the strongest effects earlier in the disease and as disease severity progresses the relative influence of brain atrophy appears more prominent. Whether brain atrophy is independent from, or a consequence of, the subcortical ischemic lesions in the disease remains to be elucidated in future prospective trials. These results would also

suggest that all these MRI markers might serve as surrogate markers in therapeutic trials in CADASIL as well as in other types of small-vessel diseases leading to ischemic subcortical dementia.

These results are in line with recent studies which have demonstrated the important influence of brain atrophy on cognitive impairment in CADASIL and other small-vessel disease (DeCarli et al., 2007; Jouvent et al., 2007; Mungas et al., 2005; Peters et al., 2006). The mechanism of brain atrophy in CADASIL, a predominantly subcortical vascular disease, remains unclear but may be partly related to apoptotic mechanisms particularly in the cortex (Viswanathan et al., 2006a). Although the impact of the sub-cortical lesions has been demonstrated in previous studies (Buffon et al., 2006; Chabriat et al., 1999; Peters et al., 2004; Viswanathan et al., 2006b, 2007) brain atrophy may represent the “final common pathway” in the pathophysiology of this arteriopathy.

Surprisingly, although CM localization in few strategic areas was independently associated with cognitive impairment in our study, overall we did not find that cerebral localization of MRI lesions played a major role in the clinical severity of CADASIL patients. These overall results are in contrast to what has been suggested in the literature (Jokinen et al., 2005; Werring et al., 2004; Zekry et al., 2003). It may be that our inclusion of highly sensitive markers of vascular cognitive impairment such as BPF and mean-ADC in this study masked the more subtle effects of lesion localization. Although in univariate analysis, strategic LL were associated with impairment, this effect did not remain in multivariate analyses. Similar results were observed with WMH. In contrast, despite the major role of global MRI markers, both frontal and caudate localization of CM were found to have an independent impact on cognitive scores. Additionally, cau-date CM also was independently associated with a marker of executive dysfunction in our cohort.

Disability has been described in CADASIL (Peters et al., 2004) and has been associated with various clinical variables and MRI markers in different studies (Holtmannspotter et al., 2005; Lesnik Oberstein et al., 2001; Molko et al., 2002; Mungas et al., 2005; Peters et al., 2006). Our results suggest that when all these variables are taken into account, it is the BPF, load of LL and of CM that are independently related to poor functional outcome, as measured by mRS. When considered with the ensemble of MRI markers in the disease, cerebral localization does not seem to play an independent role in disability in CADASIL.

In our study, a significant association between blood pressure and disability was not found. The possible impact of SBP on clinical disability in CADASIL has been reported in previous cross-sectional and longitudinal studies (Peters et al., 2004; Viswanathan et al., 2006b, 2007). This independent effect of SBP on disability has been postulated to be mediated through its influence on mean diffusivity, brain atrophy and CM in CADASIL patients (Holtmannspotter et al., 2005; Peters et al., 2006; Viswanathan et al., 2006b, 2007). It is possible that because of the co-linearity of SBP with these MRI markers, we were unable to detect such an association in these analyses.

Our study has limitations. All of the MRI markers that were independently associated with cognitive status and functional outcome were highly correlated to each other (data not shown). Thus, we cannot exclude the introduction of bias by these intercorrelations in the multivariate regression models. However, despite these potential biases, the strength of association seen with these various MRI markers is consistent with what has been previously reported in CADASIL (Dichgans et al., 2002; Holtmannspotter et al., 2005; Jouvent et al., 2007; Molko et al., 2001; Viswanathan et al., 2006b, 2007). Secondly, although our methods of lesion localization were similar to that of ongoing studies of vascular cognitive impairment (O'Brien et al., 2006), detailed anatomical mapping (DeCarli et al., 2005) of

lesions was not performed. This may have reduced our ability to detect significant associations between the localization of certain MRI markers and clinical outcomes. As multiple statistical tests were performed, some associations may not have reached statistical significance had we corrected for multiple comparisons. Finally, our principle use of measures of global cognitive function may have failed to detect significant associations with certain MRI markers. Future studies using measures for specific cognitive domains such as executive function are necessary.

In summary, our results show that among the MRI markers in CADASIL, the amount of cerebral atrophy, volume of lacunar lesions, degree of microstructural loss together with the number and location of cerebral microhemorrhages are the most strongly associated with cognitive decline and disability in this model of “pure” vascular dementia. Although these relationships remain to be definitively confirmed in future prospective studies, these results suggest that these markers may play a similar role in sporadic cerebral small-vessel diseases of the brain and thus should be strongly considered in future studies of vascular cognitive impairment. Prospective studies, which examine the temporal relationship of these lesions, should help to further define the pathophysiology underlying these observed associations.

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Table 1

Baseline characteristics of subjects in cohort.

Characteristic	<i>n</i> = 147	
	<i>n</i>	%
Sex		
Male	63	42.9
Female	84	57.1
Age (yrs±SD)	51.8±11.2	
History of hypertension	27	18.5
Past or current smoker	72	49.0
Diabetes mellitus	4	2.7
History of hypercholesterolemia	63	43.2
High school education	87	62.1
MDRS (mean±SD)	131.7±21.1	
MMSE (mean±SD)	25.5±6.2	
SBP (mmHg±SD)	128.6±16.6	
DBP (mmHg±SD)	75.5±10.1	
Mean-ADC (mm ² /s±SD)	12.2±1.6	
BPF	80.7±6.2	
nWMH	7.7±4.9	
nLV	0.085±0.15	
Number of CM	3.9±15.6	

Values are mean±SD or *n* (%). MDRS, Mattis dementia rating scale; MMSE, mini-mental status examination; SBP, systolic blood pressure; DBP, diastolic blood pressure; nWMH, normalized white matter hyperintensity; nLV, normalized lacunar lesion volume; CM, cerebral microhemorrhages.

Table 2
Univariate analysis of the effect of MRI markers on cognition and disability in CADASIL.

	nWMH		nLV		Number of CM		BPF		Mean-ADC	
	Mean (se)	p-Value	Mean (se)	p-Value	Mean (se)	p-Value	Mean (se)	p-Value	Mean (se)	p-Value
MADRS score										
1st quartile (highest score)	8.7 (0.8)	0.05	0.12 (0.01)	0.0008	14.2 (2.9)	0.001	76.4 (1.0)	<0.0001	13.1 (0.3)	0.0004
2nd quartile	8.6 (0.7)		0.08 (0.01)		0.30 (2.7)		80.8 (0.8)		11.9 (0.2)	
3rd quartile	6.9 (0.8)		0.06 (0.01)		0.24 (2.9)		81.9 (0.9)		12.3 (0.3)	
4th quartile (lowest score)	6.2 (0.7)		0.04 (0.01)		-0.38 (2.4)		83.4 (0.8)		11.6 (0.2)	
mRS score ≥ 3										
No	7.5 (0.4)	0.42	0.06 (0.01)	0.0004	0.49 (1.4)	<0.0001	81.8 (0.5)	<0.0001	12.0 (0.1)	<0.0001
Yes	8.2 (0.8)		0.18 (0.03)		13.9 (2.7)		75.6 (1.0)		13.3 (0.3)	

Analysis of covariance adjusted for age and gender. MDRS, Mattis dementia rating scale; mRS, modified Rankin scale; nWMH, normalized white matter hyperintensity; nLV, normalized lacunar lesion volume; CM, cerebral microhemorrhages; BPF, brain parenchymal fraction; ADC, apparent diffusion coefficient.

Table 3

Strategic or non-strategic localization of MRI lesions and cognitive impairment.

MRI marker	n	MDRS score (se)	p-Value [‡]
White matter hyperintensities ^a			
None	0		
Non-strategic	0		NA
Strategic	134	131.6 (1.8)	
Lacunar lesions ^a			
None	11	135.9 (5.5)	0.70
Non-strategic	14	134.7 (5.0)	
Strategic	107	131.8 (1.8)	
Cerebral microhemorrhages			
None	91	134.3 (2.0)	0.04
Non-strategic	18	131.4 (4.5)	
Strategic	29	123.5 (3.7)	

Strategic and non-strategic location of lesions were determined as outlined in the Section 2 (see text for details); se, standard error; NA, not applicable.

^a WMH was not available in 4 patients and lacunar lesions were not available in 6 patients.

[‡] Adjusted for age and sex.

Table 4

Multivariable modeling of influence of lesion burden on cognitive function and disability in 147 CADASIL patients.

Step	Variables	Beta	p-Value	Total explained variance	Standardized beta
Global cognitive function (MDRS)					
1	BPF	1.37	<0.0001	0.35	0.40
2	LL	-53.8	0.0057	0.42	-0.21
3	Mean-ADC	-2.73	0.0117	0.53	-0.21
MDRS-initiation					
1	BPF	0.50	<0.0001	0.42	0.39
2	LL	-24.8	0.0002	0.50	-0.26
3	Mean-ADC	-0.86	0.0228	0.53	-0.17
4	Age	-0.10	0.0447	0.55	-0.15
Disability (mRS)					
1	BPF	-0.12	<0.0001	0.38	-0.46
2	LL	6.19	<0.0001	0.51	0.33
3	CM	0.05	0.0017	0.55	0.21

MDRS, Mattis dementia rating scale; CM, cerebral microhemorrhage; LL, lacunar lesion volume; WMH, white matter hyperintensities; mean-ADC, mean adjusted diffusion coefficient; BPF, brain parenchymal fraction. Variables were added to the model in a stepwise fashion. Total explained variance describes total variance as variables are progressively added to the model.