Disease progression and high field MRI in CADASIL

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Chapter 3

Lacunar infarcts are the main correlate with cognitive dysfunction in CADASIL

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ABSTRACT

Background and Purpose

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is caused by mutations in the *NOTCH3* gene and is clinically characterized by recurrent stroke and cognitive decline. Previous studies have shown an association between white matter hyperintensities on brain MRI and cognitive dysfunction in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. In the general population the presence of lacunar infarcts and microbleeds is also associated with cognitive dysfunction. The objective of this study was to determine to what extent lacunar infarcts and microbleeds on MRI contribute to cognitive decline in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Methods

NOTCH3 mutation analysis was performed in 62 symptomatic and asymptomatic members of 15 cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy families. Neuropsychological tests were performed on the same day as the MRI examination. MRI was semi-quantitatively scored for white matter hyperintensities, infarct lesion load, and microbleeds. Regression analysis was performed to test the association between MRI abnormalities and neuropsychological test results.

Results

Forty individuals had a *NOTCH3* mutation and 22 did not. Severity of cognitive dysfunction in mutation carriers was independently associated with MRI infarct lesion load ($P<0.05$). In contrast, WMH lesion load and microbleeds were not associated with cognitive dysfunction after correcting for age.

Conclusions

Lacunar infarct lesion load is the most important MRI parameter associated with cognitive dysfunction in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

INTRODUCTION

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary microangiopathy caused by mutations in the *NOTCH3* gene.(1) The microvascular changes are systemic, but the cerebral vasculature carries the brunt of the pathology.(2) Clinical hallmarks are recurrent stroke, cognitive decline, migraine with aura (in up to 40% of patients), and mood disorders (up to 30%).(3) MRI invariably reveals characteristic white matter hyperintensities (WMHs) with or without lacunar infarctions and microbleeds in symptomatic, as well as asymptomatic adult mutation carriers (MCs).(4;5)

Cognitive deficits have been demonstrated from the age of 35.(3;6) In >80% of the patients a marked and progressive cognitive decline occurs before the age of 60.(3)

Because common causes of dementia, like Alzheimer dementia, do not play a significant role at this age, it is highly likely that in these subjects cognitive decline is caused by CADASIL-specific cerebral damage.

In the general population, there is evidence that cognitive dysfunction may be associated with white matter abnormalities and (silent) lacunar infarcts.(7-9) One study reported a relation between executive cognitive dysfunction and microbleeds in the frontal lobe and basal ganglia.(10)

Several studies have been performed to investigate the association between neuroimaging measures and global cognitive function in CADASIL. Most of these focused on the presence of WMHs or on quantitative MRI measurements such as diffusion tensor imaging or magnetization transfer imaging.(11-14) Whether there is an association between lacunar infarcts or microbleeds with cognitive dysfunction in CADASIL is currently unknown.

The aim of the present study is to investigate the MRI correlates of cognitive decline in CADASIL with a special focus on lacunar infarcts and microbleeds.

METHODS

Patients

We included 62 symptomatic and asymptomatic members from 15 unrelated families, of which at least the index patient had genetically confirmed CADASIL. Persons who were unable to give informed consent were not included in the study. *NOTCH3* mutation carriership was determined in all individuals by direct sequencing analysis, according to previously

described techniques.(15) The genetic status of asymptomatic individuals was not disclosed, unless specifically requested via a clinical geneticist. Controls consisted of family members at 50% carrier risk who agreed to participate but proved not to be *NOTCH3* mutation carriers. Clinical, neuropsychological, and radiological examinations were completed before mutation analysis (except for the index case), and all tests were performed blinded to *NOTCH3* mutation status.

We took a full medical history of all participants and obtained their medical records from their physicians and general practitioners. The medical ethics committee of the Leiden University Medical Center approved the study and all participants gave informed consent.

Neuropsychological Assessment

All individuals followed a standardized neuropsychological test battery, lasting 3 hours. Details regarding administration, scoring, and clinical value of the administered neuropsychological tests have been extensively described by Spreen and Strauss.(16) Global cognitive functioning was assessed using the Cambridge Cognitive Examination (CAMCOG),(17) which incorporates the Mini Mental State Examination.(18) The CAMCOG provides a total score for global cognitive functioning as well as subscores for specific cognitive functions (orientation, attention, memory, language, praxis, gnosis, calculation, abstract thinking). Memory was additionally evaluated using the Wechsler Memory Scale.(19) For testing of executive function we used Trail Making Test B,(20) and the color-interference section of the Stroop Color and Word test.(21)

For data analysis we used Mini Mental State Examination and CAMCOG as overall scores, and we used the subtests that correspond to the 5 domains of cognition according to the Diagnostic and Statistical Manual of Mental Disorders classification: language, gnosis, praxis, memory, and executive function.(22) Raw scores of the tests were used, except for the Wechsler Memory Scale "memory quotient," which was conventionally transformed into a scaled score.(16)

MRI

Image Acquisition

A uniform MRI protocol was performed on a 1.5-T MR system (Philips Medical Systems) on the same day as the neuropsychological testing. Conventional T1-weighted spin echo images (slice thickness 6 mm with a 0.6-mm interslice gap, TR/TE 600/20 ms, matrix 256x205, and a field of view 220x165 mm), dual echo T2-weighted spin echo images (slice thickness 3 mm without interslice gap, TR/TE1/TE2 3000/27/120 ms, matrix 256x205, field of view 220x220 mm), and fluid-attenuated inversion recovery images (slice thickness 3 mm without interslice

gap, TR/TE 8000/100 ms, inversion time 2000 ms, matrix 256x192, field of view 220x176 mm) were obtained. To specifically detect cerebral microbleeds, T2*-weighted gradient echo planar imaging was performed (6.0/0.6 mm, TR/TE 2598/48 ms, 256x192, echo planar imaging factor 25). All images were performed in the axial plane parallel to the inferior border of the genu and splenium of the corpus callosum.

Image Postprocessing

WMHs were defined as white matter areas with increased signal intensity on both T2-weighted and fluid-attenuated inversion recovery-weighted images. WMH volume measurements were performed on dual spin-echo images by one observer, using locally developed semiautomated segmentation software that combines knowledge-based fuzzy clustering and region-growing techniques.(23) The software computes an additional T2/proton density image to distinguish the lesions from cerebrospinal fluid. Volume of WMH was corrected for total brain volume by dividing the individual volume of WMH by intracranial volume and expressed in percent. The whole postprocessing procedure yielded an intraclass correlation coefficient of >0.99 (95% CI, 0.96 to 1.0) in an analysis of data sets from 10 patients examined twice by the same observer who performed the automated segmentation.

The number of lacunar infarcts and microbleeds were counted on hardcopies by an experienced neuroradiologist (M.v.B.) who was blinded to all patient data. A second observer (M.L.) reviewed the scores and in case of conflicting scores agreement was reached with a third observer (J.v.d.G.).

Lacunar infarcts were defined as parenchymal defects not extending to the cortical gray matter, with a signal intensity corresponding to that of cerebrospinal fluid on all pulse sequences and a diameter >2 mm. Areas that were isointense to cerebrospinal fluid on all pulse sequences, located in the lower third of the corpus striatum of the basal ganglia, and smaller than 2 mm in diameter were excluded to differentiate lacunar infarcts from normal dilated perivascular spaces.(24)

Microbleeds were defined as focal areas of signal loss on T2-weighted spin echo images that increased in size on the T2*-weighted gradient echo planar images ("blooming effect"). In this way, microbleeds were differentiated from areas of signal loss based on vascular flow void. Areas of symmetric hypointensity in the basal ganglia likely to represent calcification or nonhemorrhagic iron deposits were disregarded. Finally, to differentiate microbleeds from other intra-axial lesions with a hemorrhagic component, only areas of signal loss that were not locally associated with other abnormalities were counted as microbleeds.

Statistics

Statistical analysis was performed using the SPSS-11 statistical software package (SPSS Inc). Differences between MCs and non-MCs in demographic variables, neuropsychological test results, and MRI parameters were analyzed using Student t tests and Mann-Whitney *U* tests for continuous variables and χ^2 tests for categorical variables. Pearson correlation coefficients were used to determine the association between age and total CAMCOG scores in MCs and non-MCs. Multiple linear regression was used to determine the association between the MRI parameters and neuropsychological test results, corrected for potential confounding by age. To determine the association between each independent MRI parameter (WMHs, lacunar infarcts, microbleeds) and cognitive tests, we also used a stepwise regression model in which age was included in the first step, and in the second step WMHs, lacunar infarcts, and microbleeds (forward selection). Significance thresholds were set at $P<0.05$.

RESULTS

Patients

We confirmed a *NOTCH3* mutation in 40 of the 62 individuals. Per family, the number of participants ranged from one to 11 members. Thirty-three of the 40 MCs had neurological symptoms, ranging from 1 transient ischemic attack to multiple strokes and cognitive deficits.

Demographic characteristics, neuropsychological test results, and radiological parameters of the MCs and non-MCs are represented in Table 1. The CAMCOG total score of MCs was associated with age ($r=-0.46$, $P=0.03$), whereas no association between age and CAMCOG total score was found in non-MCs.

Of the 29 patients with 1 or more lacunar infarcts on MRI, 22 had a history of clinical stroke, 5 had CADASIL-related symptoms but no history of stroke, and 2 were asymptomatic.

The association between MRI measures and neuropsychological test results are shown in Table 2 and Table 3. Without correcting for age, infarcts were significantly associated with the neuropsychological test results of global cognitive functioning and with 4 of the 5 cognitive domains: language, praxis, memory, and executive function. WMH volume was associated with global cognitive functioning and with the domains language, praxis, memory, and 1 test of executive function. Microbleeds were not associated with function in any of the cognitive domains. After correcting for age, a significant association was found between infarct lesion load and all cognitive domains, except for gnosis and the Stroop interference subtest for executive function. Only 1 association (CAMCOG language) between WMHs and neuropsychological test results remained significant after correcting for age ($P=0.03$).

Table 1 Characteristics of the study subjects

		non-MC (n = 22)	MC (n = 40)	p
Demographics	Male/female	10/12	19/21	0.94
	Age (years (SD))	40 (13)	46 (11)	0.05
	Education (years (SD))	5.3 (3.5)	5.4 (3.7)	0.97
Cognitive Domain	Measure (score (SD))			
- Global	- MMSE	28 (1)	26 (4)	0.05
	- CAMCOG total	94 (5)	88 (15)	0.15
- Language	- CAMCOG language	27 (2)	25 (6)	0.46
- Gnosis	- CAMCOG gnosis	10 (0.5)	9 (1)	0.03
- Praxis	- CAMCOG praxis	11 (1)	11 (2)	0.20
- Memory	- WMS-MQ	111 (15)	101 (18)	0.23
- Executive Function	- Trails B (s)	84 (40)	111 (93)	0.35
	- Trails B (e)	0.4 (1)	0.4 (0.7)	0.30
	- Stroop interference (s)	98 (21)	109 (40)	0.40
MRI characteristics	WMH volume (%, SD)	0 (0)	8.2 (5.8)	<0.001
	Infarcts (#, SD)	0 (0)	8.4 (12)	<0.001
	Microbleeds (#, SD)	0 (0)	2.2 (6.2)	0.008

Chi-square test used for categorical variable male/female. Two-sample t-test used for continuous variables age, education years and WMS-MQ. Mann-Whitney U test used for the other continuous variables.
Education in years of secondary education.
Not all MCs completed the entire test protocol, due to insufficient cognitive function. The WMS and digit symbol test were completed by 37 individuals, Trails B by 33, and Stroop color/word test by 30.
The WMH volume of one individual could not be calculated due to a data reading error by the segmentation software.

Table 2 Correlations between MRI parameters and degree of cognitive dysfunction in mutation carriers.

Cognitive Domain	Measure	Infarcts		WMH volume*		Microbleeds	
		r	p	r	p	r	p
- Global	- MMSE	-0.61	<0.001	-0.38	0.017	-0.24	n.s.
	- CAMCOG total	-0.53	<0.001	-0.42	0.008	-0.24	n.s.
- Language	- CAMCOG language	-0.53	<0.001	-0.53	0.001	-0.14	n.s.
- Gnosis	- CAMCOG gnosis	-0.29	n.s.	-0.27	n.s.	-0.20	n.s.
- Praxis	- CAMCOG praxis	-0.57	<0.001	-0.41	0.010	-0.23	n.s.
- Memory	- WMS-MQ	-0.52	0.001	-0.40	0.017	-0.03	n.s.
- Executive Function	- Trails B (s)	0.82	<0.001	0.44	0.011	0.13	n.s.
	- Trails B (e)	0.48	0.004	0.18	n.s.	0.12	n.s.
	- Stroop interference	0.42	0.02	0.33	n.s.	-0.13	n.s.

* n=39
n.s. = not significant at p=0.05 level

Table 3 Correlations between MRI parameters and degree of cognitive dysfunction in mutation carriers after correcting for age.

Cognitive Domain	Measure	Infarcts		WMH volume*		Microbleeds	
		r	p	r	p	r	p
- Global	- MMSE	-0.51	0.001	-0.12	n.s.	-0.11	n.s.
	- CAMCOG total	-0.41	0.007	-0.19	n.s.	-0.12	n.s.
- Language	- CAMCOG language	-0.43	0.006	-0.47	0.03	-0.02	n.s.
- Gnosis	- CAMCOG gnosis	-0.18	n.s.	-0.04	n.s.	-0.11	n.s.
- Praxis	- CAMCOG praxis	-0.51	0.001	-0.33	n.s.	-0.14	n.s.
- Memory	- WMS-MQ	-0.45	0.006	-0.29	n.s.	0.09	n.s.
- Executive Function	- Trails B (s)	0.78	<0.001	0.36	n.s.	0.06	n.s.
	- Trails B (e)	0.48	0.007	0.13	n.s.	0.09	n.s.
	- Stroop interference	0.28	n.s.	-0.03	n.s.	-0.28	n.s.

* n=39

n.s. = not significant at p=0.05 level

The results of the stepwise regression model are shown in Table 4. These results show that infarct lesion load is an independent predictor of cognitive dysfunction for all neuropsychological tests except for CAMCOG gnosis. WMH volume was only independently associated with CAMCOG language. There was no independent association between WMH volume and cognitive dysfunction for the other tests. Moreover, there was no significant independent effect of age in the regression model, with the exception of CAMCOG gnosis (r=–0.34, P=0.03).

Table 4 The independent association between infarct lesion load, WMH volume and microbleeds with degree of cognitive dysfunction in mutation carriers

Cognitive Domain	Measure	Infarcts		WMH volume		Microbleeds	
		r	p	r	p	r	p
- Global	- MMSE	-0.62	<0.001	-	n.s.	-	n.s.
	- CAMCOG total	-0.54	<0.001	-	n.s.	-	n.s.
- Language	- CAMCOG language	-0.36	0.025	-0.34	0.034	-	n.s.
- Gnosis	- CAMCOG gnosis	-	n.s.	-	n.s.	-	n.s.
- Praxis	- CAMCOG praxis	-0.58	<0.001	-	n.s.	-	n.s.
- Memory	- WMS-MQ	-0.54	0.001	-	n.s.	-	n.s.
- Executive Function	- Trails B (s)	0.84	<0.001	-	n.s.	-	n.s.
	- Trails B (e)	0.47	0.006	-	n.s.	-	n.s.
	- Stroop interference	0.49	0.007	-	n.s.	-	n.s.

n=39

DISCUSSION

This study shows that lacunar infarct lesion load is the most important MRI parameter associated with cognitive dysfunction in CADASIL. WMH volume, microbleeds, and age did not independently contribute to cognitive dysfunction.

This study is the first to demonstrate the central role of infarcts on cognitive dysfunction in CADASIL. An association between WMHs and cognitive dysfunction is present, but this association disappears when corrected for confounding by age. This is in line with previous studies. Three studies have claimed an association between WMH and cognition in CADASIL.(12;25;26) However, in these studies no correction for age was performed. One study that did correct for age also did not find an association between WMH volume and cognition.(13)

Previous studies have reported that the course of cognitive decline in CADASIL often follows a stepwise pattern.(3;27) Our finding that lacunar infarct lesion load is the most important MRI parameter associated with cognitive dysfunction may well underlie this stepwise decline. However, prospective studies are needed to confirm this hypothesis.

An association between diffusion tensor imaging findings (mean diffusivity, diffusion anisotropy, and mean diffusivity histograms) and cognition has been reported.(11-14) In 3 studies, this association was independent of age.(12-14) Ianucci et al found an association between whole brain magnetization transfer ratio and cognition.(28) Because diffusion tensor imaging can detect ultrastructural tissue damage even in areas that appear normal on conventional MRI,(29) it is possible that an association between diffusion tensor imaging and cognition is found, whereas there is no association between WMH volume on conventional MRI and cognition. However, because none of these studies included the presence of lacunar infarctions on MRI in their analysis, it remains unclear what the results for diffusion tensor imaging would be when the presence of lacunar infarcts were to be included in such studies.

In vascular cerebral disease in general, WMHs and lacunar infarctions are both thought to contribute to cognitive decline and dementia.(7-9) However, a limitation of studies performed in the general population is that the results are based on patients from a higher age category, in whom cognitive decline can be caused by concomitant Alzheimer dementia. CADASIL is an ideal monogenic disease model for studying this issue. Our results suggest that the impact of WMHs on cognition in chronic microvascular disease is probably less significant than that of lacunar infarcts.

An interesting option would be to analyze the independent effect on cognitive dysfunction of WMHs in the periventricular white matter versus WMHs in the deep white matter. However, in this study population it was not possible to segregate periventricular and deep WMH lesions, because the majority of the MCs had confluent WMHs that involved both periventricular and deep white matter.

We cannot exclude that WMHs contributed to cognitive dysfunction in a way that the implemented cognitive tests in our study were unable to measure. We also cannot exclude that the power of the study was not sufficient to demonstrate an effect of WMHs, independent of age and infarcts. However, the conclusion that infarcts are the most prominent predictor of cognitive dysfunction remains valid, regardless of these possible limitations.

Our data show that non-MCs had a slightly higher CAMCOG gnosis score than MCs. However, a potential limitation of the present study is that it cannot be excluded that the results of the neuropsychological tests were confounded by the, statistically insignificant, age difference between MCs and non-MCs (mean age non-MCs, 40 years; MCs, 46 years). It is unlikely, however, that differences in cognitive performance between MCs and non-MCs can be attributed to the slight age difference, especially within this age category.

In the light of possible primary or secondary prevention of cognitive decline, it is important to identify risk factors associated with lacunar infarcts in CADASIL. In the general population, lacunar infarcts are associated with cardiovascular risk factors such as hypertension. (30) Although it is unknown whether this is also the case in CADASIL, associations between cardiovascular risk factors (smoking, hypertension, and male sex) and a worse clinical outcome have been reported.(12;31;32) Further research is warranted.

Cognitive dysfunction in CADASIL seems to be mainly determined by cerebral infarct lesion load. Thus, (silent) lacunar infarctions on MRI in a CADASIL patient (and not the presence of WMHs) should alert the neurologist to the possible presence of cognitive dysfunction.

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