Magnetic resonance imaging characteristics of CADASIL

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Incipient CADASIL

FIVE

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Abstract

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is caused by mutations in the *NOTCH3* gene. Knowledge of disease expression in young adult *NOTCH3* mutation carriers (MCs) is limited. The aim of the study was to characterize clinical, neuropsychological, and radiological status in *NOTCH3* MCs younger than 35 years.

Individuals younger than 35 years who were at a 50% risk of a *NOTCH3* mutation, from our CADASIL database. Thirteen individuals, from 8 families, met the criteria. *NOTCH3* mutation carriership was determined in these individuals after completion of clinical, genetic, neuropsychological, and radiological investigations in order to be able to compare mutation carriers (MCs) to non mutation carriers (NMCs) in a double-blinded setting. Magnetic resonance images were scored according to a standardized white matter hyperintensities rating scale.

Six individuals, from five families, were MCs. Clinical symptoms consisted of migraine (with aura), stroke, and stroke like episodes. We did not find evidence for psychiatric disturbances, functional disability, or cognitive dysfunction, compared with non-MCs. Radiologically, a characteristic magnetic resonance imaging lesion pattern emerged for all MCs. This comprised white matter hyperintensities in the anterior temporal lobes, the frontal lobes, and the periventricular frontal caps.

In conclusion migraine (with aura) and stroke can present in *NOTCH3* MCs younger than 35 years; however, more importantly, physical function and cognition are intact. Possible subtle cognitive dysfunction needs to be assessed in a larger study. White matter hyperintensities on magnetic resonance imaging are characteristic, and are consistently visualized from the age of 21 years and onward. Awareness of the clinical and radiological features of CADASIL in those younger than 35 years should increase early diagnosis and allow for customized counselling of young adults from families with CADASIL.

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary microangiopathy caused by mutations in the *NOTCH3* gene[19]. Distinctive ultrastructural granular osmiophilic material in the vascular media and degeneration of vascular smooth muscle cells compose the pathological hallmark[51,85]. The clinical diagnosis of CADASIL is considered in patients with otherwise unexplained central nervous system symptoms, extensive white matter changes with or without subcortical infarctions on magnetic resonance (MR) imaging, and a family history of neurological disorders[10]. The disease presentation and natural history are diverse, but, typically, the diagnosis is made in the fifth decade of life when mutation carriers (MCs) present with recurrent stroke like episodes and/or cognitive decline. Up to 40% of persons diagnosed as having the disease have a history of migraine with aura, with onset in their mid-20s. Psychiatric disturbances can play a role in about a third of affected individuals[10].

CADASIL is considered a late-onset hereditary disease, with a mean age at onset of 45 years[8]. Abnormalities on MR imaging are present before the onset of clinical symptoms, and it is generally accepted that by the age of 35 years, all *NOTCH3* MCs have white matter hyperintensities (WMHs) to some extent[6,8,86]. Although several studies have included clinical or radiological, reports of asymptomatic MCs, these studies did not focus specifically on young adults[8,10,39,42,87]. This prompted us to prospectively study the clinical, neuropsychological, and radiological profiles of individuals younger than 35 years who were at a 50% risk of a *NOTCH3* mutation. We expect that more insight into the clinical and radiological aspects of CADASIL in young adults will improve early diagnosis in this age group and allow for more tailored counselling of asymptomatic young adults at risk for CADASIL.

Materials and methods

Subjects

Individuals participating in the study gave informed consent, and the medical ethics committee of the Leiden University Medical Centre approved the study. All those younger than 35 years who were at a 50% risk of being a carrier, irrespective of signs and symptoms, were selected from a database of 15 families with CADASIL who had a known *NOTCH3* mutation; these families were participating in an ongoing study of CADASIL in the Netherlands. Individuals younger than 18 years were not included for ethical reasons. The database included 63 symptomatic and asymptomatic individuals, of whom 13 met the inclusion criteria for the present study. These 13 individuals were

members of 8 unrelated families, with varying mutations in the *NOTCH3* gene. Clinical, neuropsychological, and radiological examinations were completed before mutation analysis. Consequently, examiners (SAJLO, YMK, HAMM, and MAvB) and participants were blinded to carrier status. Mutation analysis was performed according to previously described techniques[22]. Before the study commenced, it was agreed with participants that the results of mutation analysis and an MR examination would not be disclosed. Counselling was performed by an independent genetic counsellor for those individuals who requested presymptomatic testing.

Clinical data

We obtained a full medical history from all participants and obtained their medical records from their physicians and general practitioners. In a semistructured interview, specific questions were asked pertaining to possible undocumented past episodes of focal neurological deficits, migraine (with aura), and psychiatric history. Criteria for migraine were maintained according to the international Headache Classification Committee[88]. All participants completed a structured questionnaire concerning the presence of cardiovascular disease–related risk factors and drug use. The questionnaire included questions about nicotine and alcohol abuse, body weight and height, and history of hypercholesterolemia, hypertension, and diabetes mellitus. These conditions were defined as previously described[76]. Disability at the time of the study was measured semiquantitatively with the Rankin scale score, which ranges from 0 (no symptoms at all) to 5 (severe disability requiring constant nursing). Depression and anxiety were measured with the Hospital Anxiety and Depression Scale (HADS)[89,90]. The HADS is a 4-point, 14-item, self-assessment instrument developed for detecting levels of depression and anxiety in the setting of a hospital outpatient clinic. The global outcome measure was used, with a cut-off score of 13, because this is more appropriate than the anxiety and depression subscores in samples with minor psychiatric disorders[91].

MR imaging

A uniform MR imaging protocol was performed on a 1.5-T MR imaging system (Philips Medical Systems, Best, the Netherlands) on the same day as the neuropsychological testing. The same neuroradiologist (MAvB), blinded to clinical and genetic data, reviewed all MR scans. Labelling MR scans with a number, instead of patient name and age, further ensured blinded scoring. The MR imaging protocol and grading of WMHs and lacunar infarctions were performed as previously described[76]. In brief, T1-weighted spin-echo, dual T2-weighted turbo spin-echo, and fluid-attenuated inversion recovery images were obtained in the axial plane. White matter hyperintensity lesion load was

graded according to the validated signal hyperintensities' rating scale of Scheltens et al[59]. In this scale, the brain is anatomically divided into deep white matter, basal ganglia, and infratentorial regions. For each region, a score of 0 to 6 is assigned according to the following scale: 0, absent; 1, up to 5 WMHs with less than a 3-mm diameter; 2, 6 or more WMHs with less than a 3-mm diameter; 3, up to 5 WMHs with a 4- to 10-mm diameter; 4, 6 or more WMHs with a 4- to 10-mm diameter; 5, 1 or more WMHs with a greater than 10-mm diameter; and 6, confluent hyperintensity. In addition, frontal and occipital periventricular "caps" and periventricular "bands" are scored as follows: 0, absent; 1, up to 5 mm; and 2, greater than 5 mm. We also scored WMHs in the external capsule region, which is not normally included in the scale of Scheltens et al. We did not include this subscore in the total WMHs score. The presence of subcortical lacunar lesions, considered specific for CADASIL, was recorded[92].

Neuropsychological evaluation

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[123]. Global cognitive functioning was assessed using the Cambridge Cognitive Examination, which incorporates the Mini-Mental State Examination[94]. The Cambridge Cognitive Examination provides a total score for global cognitive functioning and subscores for specific cognitive functions (memory, orientation, language, praxis, and gnosis). In addition, memory was evaluated using the Wechsler Memory Scale. Tests of executive functioning included the Trail-Making Test B, the Stroop colour and word test, the digit symbol subtest of the Wechsler Adult Intelligence Scale–Revised, and verbal and category fluency. For data analysis, the raw scores of the tests were used, except for the Wechsler Memory Scale memory quotient and the digit symbol subtest score, which were conventionally transformed into scaled scores[123].

Statistical analysis

Statistical analysis was performed using the SPSS software package, version 10 (SPSS Inc, Chicago, Ill). Differences in mean test results between MCs and non-MCs (NMCs) were analyzed with the Student t-test.

Results

Subjects and clinical data

Of the 13 individuals at 50% carrier risk, 6 were *NOTCH3* MCs. These 6 individuals came from 5 unrelated families. The mutations were as follows: Arg141Cys (n=2), Arg153Cys (n=1), Arg182Cys (n=2), and Arg1076Cys (n=1). The mean ± SD age of the 6 MCs (2 men and 4 women) was 24.67 ± 4.32 years (range, 21-31 years), and that of the 7 NMCs (6 men and 1 woman) was 27.14 ± 3.80 years (range 22-33 years). Age (P=0.30) and sex (P=0.06) did not differ significantly between MCs and NMCs. None of the participants had visited a physician with symptoms leading to a diagnosis of CADASIL before the study, and none recalled any obvious episodes of focal neurological deficit with sudden onset. However, 2 individuals described aspecific episodes of sudden focal neurological deficits. In one individual (patient number [PN] 6), this involved speech disturbances lasting less than 1 minute, since roughly the age of 25 years; the other individual (PN 3) had experienced several weeks of blurred vision in late adolescence. Although both of these individuals had migraine with aura, these episodes did not resemble their usual auras, nor were they associated with headache. Both were MCs. A third MC (PN 4) had a confirmed stroke, consisting of sudden dysphasia and unilateral hand and tongue paresthesia, shortly after the study, at the age of 26 years. A total of 3 MCs (1 man and 2 women) had migraine, and 2 had migraine with aura. In one individual (PN 6), attacks started in the late 20s and consisted of typical visual aura followed by headache. The other individual (PN 3) had visual, sensory, and aphasic aura followed by unilateral headache, photophobia, phonophobia, and vomiting, with attacks clustering in the first 3 years of adolescence. The third individual (PN 1) had had several migraine attacks without aura, also clustering in early adolescence. At the time of the study, no focal neurological deficits were clinically observed in any of the participants. The Rankin scale score was 0 (no disability at all) for all MCs and NMCs. Cardiovascular risk factors were present as follows: diabetes mellitus, hypertension, and alcohol abuse in 0 MCs and NMCs; smoking in 4 of 7 NMCs and in 0 MCs (P=0.02); and hypercholesterolemia in 1 of 7 NMCs and in 0 MCs (P=0.38). The body mass index was not increased in either MCs or NMCs. Two MCs and 1 NMC had a history of minor depression in their early 20s, for which psychological help was sought. One NMC and 0 MCs had a global HADS score higher than 13. The mean ± SD global HADS score for MCs was 5.1 ± 3.8; and for NMCs, 7.4 ± 6.3 (P=0.46).

Table 1 WMHs scores in MCs and NMCs younger than 35 years

	MCs (n=6)						NMCs (n=7)							P
Variable	1	2	3	4	5	6	1	2	3	4	5	6	7	
Age, y	≤23	≤23	≤23	≤26	≤29	≤32	≤23	≤23	≤29	≤29	≤29	≤32	<35	.3
Periventricular WMHs (0-2)														
Caps														
Frontal	0	1	1	2	2	2	0	0	0	0	0	0	0	.001
Occipital	0	0	0	0	1	1	0	0	0	0	0	0	0	.10
Bands: lateral ventricles	0	1	1	1	1	2	0	0	0	1	1	1	1	.20
Sum score (0-6)	0	2	2	3	4	5	0	0	0	1	1	1	1	.01
Subcortical WMHs (0-6)														
Frontal	1	3	0	4	3	6	0	0	0	0	0	3	0	.02
Parietal	0	0	0	3	3	6	0	0	0	0	0	0	0	.05
Occipital	0	0	0	6	0	0	0	0	0	0	0	0	0	.30
Temporal	3	5	5	3	3	6	0	0	0	0	0	0	0	<.001
Sum score (0-24)	4	8	5	16	9	18	0	0	0	0	0	3	0	.001
Basal ganglia WMHs (0-6)														
Caudate nucleus	0	0	0	0	0	0	0	0	0	0	0	0	0	NA
Putamen	0	0	0	0	0	0	0	0	0	0	0	0	0	NA
Globus pallidus	0	0	0	0	0	0	0	0	0	0	0	0	0	NA
Thalamus	0	0	0	0	0	1	0	0	0	0	0	0	0	.30
Sum score (0-36)	0	0	0	0	0	1	0	0	0	0	0	0	0	NA
Internal capsule	0	0	0	0	0	0	0	0	0	0	0	0	0	.30
External capsule region†	0	0	0	1	0	1	0	0	0	0	0	0	0	.10
Infratentorial WMHs (0-6)														
Cerebellum	0	0	0	0	0	0	0	0	0	0	0	0	0	NA
Mesencephalon	0	0	0	0	0	0	0	0	0	0	0	0	0	NA
Pons	0	0	0	0	0	5	0	0	0	0	0	0	0	.30
Medulla	0	0	0	0	0	0	0	0	0	0	0	0	0	NA
Sum score (0-24)	0	0	0	0	0	5	0	0	0	0	0	0	0	.30
Total WMHs Score	4	10	7	19	13	29	0	0	0	1	1	4	1	.004

MCs = mutation carriers, NMCs = . non-mutation carriers, WMHs = white matter hyperintensities. To ensure patient confidentiality, sex was not specified for each patients individually.† The subscore for this region was not included in the total WMHs score because WMHs in this\ region are not normally included in the scale of Scheltens et al.

MR imaging

Table 1 shows an overview of WMHs scores according to Scheltens et al.[59] The mean ± SD total WMHs score in MCs was 13.67 ± 9.10 (range, 4-29), vs. 1.00 ± 1.40 (range, 0-4) in NMCs (P=0.004). None of the MCs or NMCs had (subcortical) infarctions on MR imaging. One MC had subcortical lacunar lesions, abutting temporal lobe WMHs.

Table 2 Neuropsychological test results

Cognitive Domain	Measure	MCs (n = 6)	NMCs (n = 7)
Global cognitive functioning	CAMCOG	99 (1)	94 (3)
	MMSE	30 (1)	29 (1)
Memory	CAMCOG memory	23 (1)	22 (1)
	WMS memory quotient	116 (8)	108 (11)
	WMS verbal memory	11 (3)	9 (2)
	WMS picture memory	12 (1)	12 (1)
Language	CANCOG language	29 (1)	27 (2)
Praxis	CAMCOG praxis	12 (1)	11(1)
Gnosis	CAMCOG gnosis	10 (0)	10 (0)
Executive functioning	word fluency (animals)	56 (8)	42 (14)
	category fluency (animals)	24 (2)	22 (4)
	TMT b (seconds)	49 (10)	76 (27)
	TMS B (errors)	0.1 (0.4)	(0.4)
	Stroop colour/word (seconds)	71 (4)	87 (16)
	Stroop colour/word (errors)	0 (0)	1 (1)
	Stroop interference (s)	23 (6)	30 (12)
	digit symbol (seconds)	63 (13)	57 (10)

Data are presented as mean (SD). CAMCOG = Cambridge Cognitive examination; MMSE = mini mental state examination; WMS = Wechsler Memory scale; TMT = Trail Making Test. T-test did not reveal any significant (P<0.01) differences between mutation carriers (MCs) and non-mutation carriers (NMCs)

A distinct pattern of WMHs emerged in MCs, consisting of deep WMHs of the temporal lobes (6 of 6 individuals), frontal lobes (5 of 6 individuals), and frontal periventricular caps (5 of 6 individuals). Figure 1 shows MR scan results. The WMHs of the temporal lobe were specifically located in the anterior pole. Next to being present in all MCs, temporal lobe WMHs were also the most extensive, with a mean ± SD WMHs score of 4.20 ± 1.30 (range, 3-6), followed by a score of 2.80 ± 2.14 (range, 0-6) for the frontal lobe. Basal ganglia and infratentorial WMHs were seen only in the MC older than 30 years (table 1). Two MCs had

WMHs in the external capsule region. Periventricular bands were seen in 5 of 6 MCs, but these were also relatively frequent in NMCs (4 of 7 individuals). One NMC had a frontal subcortical WMHs that could be attributed to head trauma experienced 1 year previous to the present MR investigation.

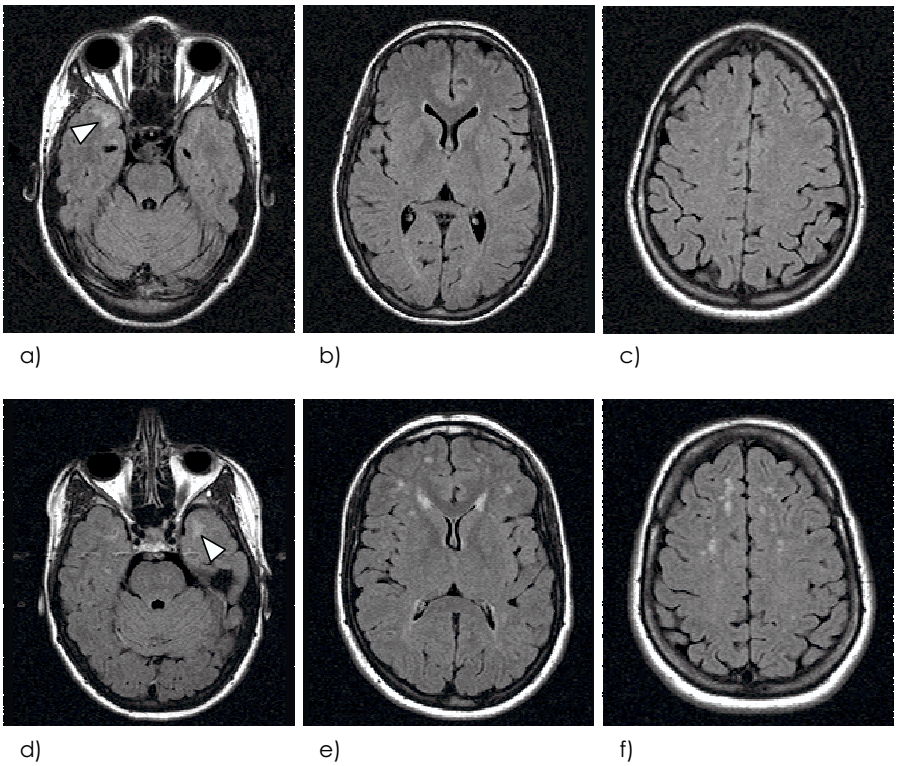

Figure 1 FLAIR MR images of 2 mutation carries(a-c, d-f respectively). Axial slices are shown through the level of the temporal lobes, the basal ganglia, and the centrum semiovale in individuals ages 21 and 31 years. In both individuals, hyperintensities are seen in the anterior temporal lobe (arrowheads in a and d), and both have frontal caps. Imaging of the 31-year old individual illustrates the typical pattern of frontal lobe hyperintensities that can be seen in CADASIL mutation carriers younger than 35 years

Neuropsychological evaluation

The neuropsychological test results are represented in table 2. The MCs and NMCs did not differ in mean years of education after primary school (8 and 7 years, respectively) or in level of education. There was no significant difference in global or specific neuropsychological functioning between MCs and NMCs.

Discussion

The aim of this study was to learn more about the status of young adult *NOTCH3* MCs. Clinical, neuropsychological, and radiological data were compared between *NOTCH3* MCs and NMCs younger than 35 years, in a setting blinded to MC status. Inherent to the study of a subgroup with a comparatively rare disease, this study was hampered by a relatively small study population. However, to our knowledge, it is the first to simultaneously and comprehensively study all relevant disease features in this age group. Furthermore, the lack in numbers is partially compensated by the multipedigree background of the participants and the presence of a highly representative control group of family members without a *NOTCH3* mutation. Follow-up of this patient cohort will be performed, and should provide further knowledge of the natural history of disease in young *NOTCH3* MCs.

The main result is that there was no quantifiable physical or cognitive impairment in young adult *NOTCH3* MCs. Disease expression was confined to migraine (with aura) and, less frequently, stroke. The MR scans showed a characteristic pattern of early WMHs. Migraine (with aura) was more common in MCs than in NMCs (3 of 6 vs. 0 of 7 individuals) presenting in the second and third decades of life. This confirms that migraine (with aura) can be an early disease manifestation of CADASIL[8,10,95]. Stroke presented in 1 MC at the age of 26 years (shortly after the study), and 2 MCs described atypical episodes of immediate-onset focal neurological deficits, of possible ischemic origin. In 2 multifamily studies of the CADASIL phenotypic spectrum, ischemic episodes are reported to occur at the mean ± SD ages of 49.3 ± 10.7 years5 and 46.1 ± 9.0 years (range, 30-66 years)[10]. However, from this study population, and from our clinical experience, we find that transient ischemic attacks and stroke can already present in the third decade of life, although most do not lead to permanent dysfunction. There were no psychiatric disorders, as defined by the medical history and the HADS score. The age at onset of psychiatric disorders in individuals with CADASIL has not been defined, but from our results, we conclude that these are not present before the age of 35 years. An extensive neuropsychological assessment did not reveal any differences in cognitive function between MCs and NMCs. Taillia et al studied neuropsychological function in 8 individuals without dementia, aged 35 to 66 years, who had neurologically symptomatic CADASIL, and found subtle cognitive impairment in all, specifically in tasks involving the frontal lobes[96]. We did not find any dysfunction concerning these executive tasks, or any other tasks, in those younger than 35 years. The age of 35 years, therefore, may be the lower age limit at which neuropsychological dysfunction can begin to become manifest. Possible subtle cognitive changes in this age group need to be assessed in a larger follow-up study.

The MR imaging abnormalities in young adult *NOTCH3* MCs, although relatively subtle in the early 20s, were consistently present much earlier than the maintained age of 30 to 35 years[8,86]. Furthermore, the MR lesion pattern proved to be distinct, with landmark features being anterior temporal lobe WMHs, frontal lobe WMHs, and frontal caps. Temporal lobe lesions were present in all MCs, with a WMHs score between 3 and 6, corresponding to the presence of at least 1 lesion of 4 mm in diameter. The scale of Scheltens et al does not reflect the sublocation of WMHs within the cerebral lobes, but we observed that the temporal lobe lesions were specifically located anteriorly[59]. In the general population with CADASIL, temporal lobe WMHs are often, but not always, present (sensitivity, 95%; and specificity, 80%)[43]. Frontal caps and frontal deep WMHs were seen in 5 of 6 MCs, although the latter were not specific for MCs, because one NMC also had frontal WMHs. Another nonspecific MR imaging feature was lateral periventricular bands, which were observed in MCs and NMCs. Subcortical lacunar lesions, although apparently infrequent in individuals younger than 35 years (1 of 6 MCs), are a specific sign for CADASIL[92]. Overall, our MR findings correspond with those of recent studies describing periventricular, temporal pole, frontal lobe, and external capsule region WMHs as radiological markers in (older) patients with CADASIL[39,41,43]. White matter hyperintensities in older patients, however, are much more extensive, with the heaviest lesion load in the frontal lobes,24 constituting a visually altogether different MR result from the one we observed in young MCs[41]. Furthermore, contrary to what has been previously suggested, we did not find external capsule region WMHs to be a distinguishing feature early in the radiological disease process[43]. We have no clear-cut answer as to why CADASIL-related WMHs initiate in the temporal and frontal lobes. Apparently, certain vessels may be more susceptible to CADASIL-related vasculopathy than others, possibly for reasons of calibre or length[43]. At any rate, acquaintance with the WMHs lesion pattern and load in those younger than 35 years should be an important means of recognizing CADASIL in this age group, especially in the differential diagnosis of multiple sclerosis, which can mimic the signs and symptoms of CADASIL[49,97]. Once the diagnosis of CADASIL is considered based on clinical and neuroimaging data, *NOTCH3* mutation analysis or pathological examination of a skin biopsy specimen is required to confirm the diagnosis[66,98].

Familiarity with the clinical and neuroimaging features of CADASIL in young adults should promote early diagnosis and prevent misdiagnosis and needless (invasive) diagnostic or therapeutic procedures.