Positron Emission Tomography Examination of Cerebral Blood Flow and Glucose Metabolism in Young CADASIL Patients

Susanna Tuominen, MD; Qing Miao, MSc; Timo Kurki, MD, PhD; Seppo Tuisku, MD; Minna Pöyhönen, MD, PhD; Hannu Kalimo, MD, PhD; Matti Viitanen, MD, PhD; Hannu T. Sipilä, MSc; Jörgen Bergman, PhD; Juha O. Rinne, MD, PhD

Background and Purpose—CADASIL causes repeated ischemic strokes leading to subcortical vascular dementia. The purpose of this study was to assess whether cerebral blood flow (CBF) and regional cerebral metabolic rates of glucose ($rCMR_{gluc}$) in CADASIL patients are affected in early adulthood.

Methods—CBF and $rCMR_{gluc}$ were examined with positron emission tomography in correlation with magnetic resonance imaging (MRI) in 14 adult (19 to 41 years) CADASIL patients with the *Notch3* R133C mutation. Seven patients had experienced transient ischemic attack and 3 had experienced ≥1 strokes.

Results—The mean CBF in the CADASIL patients was significantly lower in both frontal ($P=0.019$) and occipital ($P=0.009$) white matter (WM) than those in the controls. CBF decreased significantly with increased severity of the disease. The patients had lower mean $rCMR_{gluc}$ values than the controls, although differences were not statistically significant. Sum scores of semiquantitative MRI rating scale (Scheltens) correlated significantly with WM CBF but not with $rCMR_{gluc}$.

Conclusions—In CADASIL, there is an early and significant decrease in the CBF of WM associated with simultaneous MRI changes. These are obviously caused by the arteriopathy in long penetrating arteries and indicate early tissue damage, also expressed as impaired $rCMR_{gluc}$ in the WM. **(*Stroke*. 2004;35:1063-1067.)**

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a progressive disease of small and medium arteries caused by mutations in the *Notch3* gene,[1,2] which lead to degeneration of vascular smooth muscle cells in arteries throughout the body, although the clinical symptoms are only neurological. CADASIL is characterized by recurrent ischemic episodes and cognitive decline leading to subcortical vascular dementia. In addition, migraine with aura or psychiatric disorders occur in ≈one third of the patients.[3,4] Magnetic resonance imaging (MRI) of CADASIL patients shows characteristic periventricular white matter (WM) hyperintensity in T2-weighted (T2w) images in asymptomatic CADASIL patients.[5] Later T1-weighted (T1w) images disclose multiple lacunar infarcts in WM and deep gray matter (GM), the volume of which correlates with disability.[6]

In CADASIL, reduced cerebral blood flow (CBF) has been previously demonstrated with positron emission tomography (PET) in a 52-year-old homozygous patient and a 53-year-old heterozygous patient.[7] In another study, an asymptomatic CADASIL patient (age 58 years) had a 40% decrease in CBF in the cortex and WM and an increased oxygen extraction fraction but a normal cerebral metabolic rate of oxygen.[8] In the same study, a patient with dementia (age 63 years) had a more severe decrease in CBF and reduced cerebral metabolic rate of oxygen. With PET, it was recently shown that the regional cerebral metabolic rate of glucose ($rCMR_{gluc}$) is reduced in more disabled (Mini-Mental state examination [MMSE] mean value 22, Rankin mean value 2.6) CADASIL patients (mean age 55.8, range 46 to 65 years).[9]

With MRI bolus tracking, CBF and cerebral blood volume (CBV) in symptomatic elderly CADASIL patients (mean age 58 years) were significantly reduced in the T2w hyperintensity areas of WM and more severely in patients with dementia. No significant reduction in CBF and CBV was observed in cerebral cortex.[10] In another study, elderly CADASIL patients (mean age 52.3 years) had decreased regional CBV in the T2w hyperintense WM, and the CBV correlated inversely with cognitive impairment and disability.[11]

Received July 28, 2003; final revision January 8, 2004; accepted January 13, 2004.

From Department of Neurology (S.Tuominen), Turku PET Centre (S.Tuominen, H.T.S., J.B., J.O.R.), Department of Pathology (Q.M., H.K.), and Department of Radiology (T.K.), Turku University Hospital and University of Turku, Turku, Finland; Department of Neurology (S.Tuisku), Keski-Pohjanmaa Central Hospital, Kokkola, Finland; Department of Medical Genetics (M.P.), Family Federation of Finland, Helsinki, Finland; Department of Pathology (H.K.), University of Helsinki and Helsinki University Hospital, Helsinki, Finland; Department of Pathology (H.K.), Uppsala Academic Hospital and University of Uppsala, Uppsala, Sweden; Department of Geriatric Medicine (M.V.), University of Turku, Turku, Finland; Division of Geriatric Medicine (M.V.), Karolinska Institutet, Huddinge Hospital, Stockholm, Sweden.

Correspondence to Dr Hannu Kalimo, Turku University Hospital and University of Turku, Department of Pathology, FIN-20520 Turku, Finland. E-mail hkalimo@utu.fi

Stroke **is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000124124.69842.2d**

TABLE 1. Clinical Characteristics and MRI Findings in the CADASIL Patients

Patient	Age (y)/Sex	Clinical Disorders (age at the first stroke)	Rankin	MMSE	Scheltens MRI Sum Score	Lacunar Infarcts in T1w MRI
1	19/F	TIA, migraine	1	30	4	0
2	24/F	TIA	1	30	18	0
3	25/F	TIA	1	30	11	0
4	29/F	TIA	1	29	21	0
5	29/F	TIA, migraine	1	29	26	1
6	32/M	TIA, migraine	1	30	22	2
7	34/M	Asymptomatic	0	30	27	13
8	35/M	Stroke (32 y)	2	24	35	9
9	36/M	2 Strokes (30 y), migraine	2	29	41	18
10	37/F	TIA, migraine	1	30	23	11
11	37/M	Epileptic seizures	1	30	25	0
12	39/F	Psychotic episodes	2	28	29	8
13	41/F	Stroke (39 y), depression	2	26	41	20
14	42/M	Asymptomatic	0	29	23	2

To assess whether CBF and $rCMR_{gluc}$ are affected in young adult CADASIL patients, we used PET to examine 14 patients (mean age 32.7 years) who had, at most, mildly impaired cognition (mean MMSE score 29, mean Rankin score 1.1). It was of special interest to examine if the CBF and $rCMR_{gluc}$ changes appear in parallel and whether MRI findings correlated with the changes in CBF and/or $rCMR_{gluc}$.

Materials and Methods

Patients

Fourteen CADASIL patients from 6 families (8 females and 6 males, mean age 32.8±6.7, range 19 to 41 years) who had a confirmed C475T (R133C) *Notch3* mutation were examined. Neurological and PET examinations were performed on the same day and MRI investigation was performed within 1 month of the PET examination. The degree of disability was graded according to the Rankin scale.[12] Cognitive status was assessed with MMSE.[13] The demographic data are presented in Table 1.

Controls

Nine healthy volunteers (5 females and 4 males with a mean age 37.4±6.1 years, range 28 to 45 years) served as control subjects for the CBF study. Similarly, 16 healthy controls (9 females and 7 males; mean age 45.3±10.4 years, range 28 to 61) were studied for rCMRgluc. Five of the control subjects investigated for CBF and $rCMR_{gluc}$ were healthy members of CADASIL families who were confirmed to not have the *Notch3* mutation. None of the controls had a history of neurological disorder and all had normal T1w and T2w MRI. The ethical committee of Turku University Hospital approved the study and all the subjects had given their informed consent.

PET Procedure

PET images were performed in a softly lit and quiet room using a GE Advance PET scanner (General Electric Medical Systems, Milwaukee, Wis) with the 2-dimensional scanning mode. The subjects were positioned in the PET scanner with the orbitomeatal line parallel to the detector rings. The axial and transaxial spatial resolution of the reconstructed images was approximately 5-mm full-width at half maximum.

The procedure for the synthesis and the automated method for the application of the ^{15}O-labeled water has been described previously.[14] On average, 1.3 GBq ^{15}O-labeled water was administered intravenously and a parametric CBF image was attained by an autoradiographic method[15] with a 90-second integration time. For rCMRgluc examination, 2-[18F]-fluoro-2-deoxy-D-glucose ([18F]FDG) was synthesized according to the earlier published methods.[16,17] The radiochemical purity exceeded 95%; 3.7 MBq/kg (0.1 mCi/kg) was injected intravenously ≈10 to 15 minutes after termination of CBF examination and a dynamic scan for 55 minutes was acquired. During the PET study, arterial blood samples were drawn from the arterial cannula inserted in the radial artery.

The regions of interest (ROI) were identified and placed individually in the patient and control MRI scans, which were then matched with PET images using a surface-fitting method[18] and resliced according to PET images using trilinear interpolation. The ROIs were then copied on CBF and $rCMR_{gluc}$ examinations on both hemispheres in 17 transaxial planes. Circular ROIs were drawn on the frontal and occipital WM periventricularly on top of ventricles or just above the ventricle level in 4 planes. In addition, ROIs were drawn on the frontal, temporal, and sensorimotor cortical structures. ROIs were also placed on the hippocampus, putamen, and cerebellum. The rCMRgluc values in mol/mL per minute were calculated using the graphical analysis method described originally by Patlak and Blasberg.[19]

MR Imaging

All the CADASIL patients and control subjects were studied by MRI. Six patients were examined using 1.5 T Siemens Magnetom MR equipment. The MR study consisted of axial T2w spin-echo 3120/90 (repetition time/echo time) images with slice thickness of 5 mm and T1w sagittal 3-dimensional MPR (magnetization-prepared rapid-gradient echo) 10/4 images with flip angle of 10° and slice thickness of 1.5 mm. Eight patients were studied using GE Signa 1.5 T equipment. The corresponding details of axial T2w images were fast spin-echo 4520/81.6, slice thickness of 5 mm, T1w axial 3-dimensional fast spoiled gradient echo sequence, and 11.3/4.2 images with slice thickness of 1.2 mm. All the controls were examined using the same 1.5-T MR equipment. The T2w MRI images were graded according to a validated semiquantitative rating scale of Scheltens et al[20] (maximum sum score=78 points), and the number of lacunar infarcts were calculated in T1w images by the neuroradiologist (T.K.).

Statistical Analysis

The mean of left and right hemisphere CBF and $rCMR_{gluc}$ values were used in the statistical analyses. Differences in CBF and

TABLE 2. Cerebral Blood Flow Values (mL · 100 g^{-1} · min^{-1}) in Regions of Interest in Patients and Controls

Patient	Age (y)/Sex	Cerebral Cortex						White Matter	
		Frontal	Sensorimotor	Temporal	Hippocampus	Putamen	Cerebellum	Frontal	Occipital
1	19/F	68.9	55.7	64.7	68.9	99.6	66.7	18.6	18.4
2	24/F	67.5	58.6	57.9	50.7	67.2	64.5	18.5	19.4
3	25/F	71.0	69.5	54.3	46.0	76.8	67.0	20.8	18.0
4	29/F	70.9	57.2	63.9	60.4	93.7	71.5	18.7	18.3
5	29/F	80.4	72.7	67.3	63.8	82.6	75.4	20.1	18.3
6	32/M	48.9	46.7	42.0	38.5	57.3	44.6	16.4	16.3
7	34/M	64.2	64.9	48.6	45.8	58.9	62.3	19.2	16.1
8	35/M	51.1	47.1	42.5	33.7	47.2	49.8	13.9	11.9
9	36/M	49.4	49.8	41.8	39.1	49.0	47.6	14.1	14.0
10	37/F	55.3	50.8	56.1	55.9	64.0	71.0	19.9	17.1
11	37/M	56.4	54.4	50.9	45.6	55.2	67.3	16.2	13.8
12	39/F	43.5	40.7	33.3	28.9	52.4	43.5	16.5	14.0
13	41/F	55.9	50.0	42.5	42.7	52.0	49.8	15.9	13.3
14	42/M	50.3	48.9	43.7	38.3	53.8	47.4	14.7	14.7
Patient average	32.8	59.5	54.8	50.7	47.0	65.0	59.2	17.4*	16.0†
SD	6.7	11.4	9.1	10.3	11.7	16.8	11.4	2.3	2.4
Control									
1	28/M	61.9	58.8	61.1	50.8	66.3	60.8	20.4	15.9
2	30/F	60.7	55.4	52.8	49.9	65.8	60.8	21.5	20.6
3	31/M	58.3	51.6	46.9	41.6	61.2	57.3	15.2	17.2
4	36/M	46.8	47.2	43.2	37.8	47.8	54.6	18.3	15.2
5	39/F	46.2	49.2	46.4	39.5	46.8	55.9	24.5	23.8
6	40/F	48.7	48.4	46.0	40.5	51.3	56.4	21.0	19.4
7	41/F	53.1	48.8	48.3	44.4	59.4	58.8	20.3	19.3
8	42/F	53.0	48.2	55.8	43.4	63.3	59.2	22.0	19.2
9	45/M	45.5	42.8	36.3	39.7	49.1	56.4	17.5	18.0
Control average	37.4	49.3	50.0	48.5	43.1	56.8	57.8	20.1*	18.7†
SD	6.1	6.0	4.7	7.3	4.6	8.0	2.2	2.7	2.6

SD indicates standard deviation.

*P=0.019. †P=0.009 (ANCOVA with age as covariate and with Bonferroni correction)

$rCMR_{gluc}$ between patients and controls were calculated using ANCOVA with age as a covariate. Bonferroni correction was used because of multiple comparisons. Correlations between age, WM MRI changes, CBF, and $rCMR_{gluc}$ in different regions were calculated with Pearson correlation test. SAS and SPSS statistical programs were used in the calculations.

Results

Clinical Data

Two patients were asymptomatic. Seven patients had had at least 1 transient ischemic attack and 3 patients had experienced ≥1 strokes. Five patients had migraine with aura. One patient had chronic psychiatric disorder and another had undergone 2 epileptic seizures in early childhood as the only manifestations. The mean value of MMSE scores in the patients was 29 (range 24 to 30 points), ie, none of them had dementia. The mean score of the Rankin scale was 1.1 (range 0 to 2, see Table 1).

Cerebral Blood Flow

In the WM, the average CBF values of the patients (adjusted for age) were significantly lower than those in the controls (in the frontal WM: F=8.25, P=0.019; in the occipital WM: F=10.36, P=0.009; Table 2). The decrease of CBF in WM with age was greater in the patients than in the controls. The age ≈30 years seemed to be a transition zone for the decrease in CBF, similar to that for the appearance of infarcts, with the first one being detected in a 29-year-old patient (Table 1). In patients younger than 30, the CBF in WM was similar to the controls (frontal WM P=1.00; occipital WM P=0.08), whereas in the patients older than 30, the CBF was significantly (frontal WM P=0.03; occipital WM P=0.002) decreased (Figure 1).

In cortex, hippocampus, putamen, and cerebellum, CBF was unexpectedly higher in the CADASIL patients than in the controls, although not significantly (Figures 1 and 2, and Table 2). In the patients, CBF in the aforementioned regions significantly decreased with the patient's age (variation in different regions r=0.54 to 0.80, P=0.04 to 0.0007). In the controls, significant association between CBF and age was observed only in sensorimotor (r=−0.89, P=0.001) and frontal (r=−083, P=0.006) cortex. In the GM, the mean CBF values of patients younger than 30 was higher than in the controls, whereas in patients older than 30 years it was lower (Figure 1).

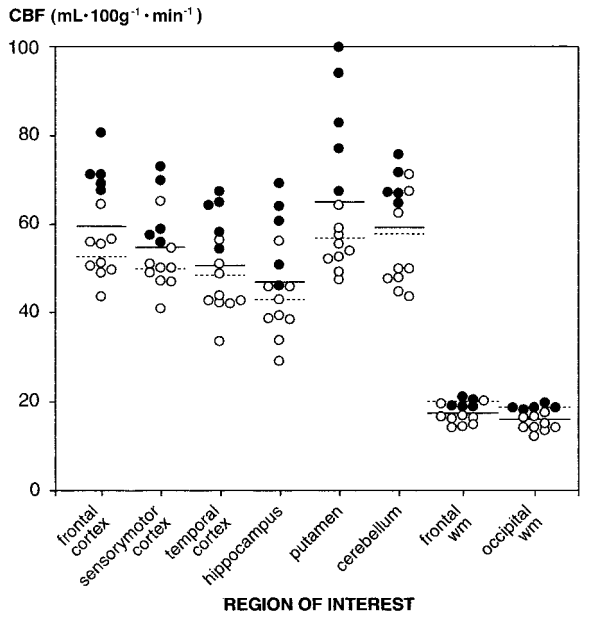

Figure 1. CBF in patients. Black circles represent patients younger than 30 years (n=5), and white circles represent patients older than 30 years (n=9). The continuous line corresponds to the average CBF of the patients and the dotted line to that of the controls.

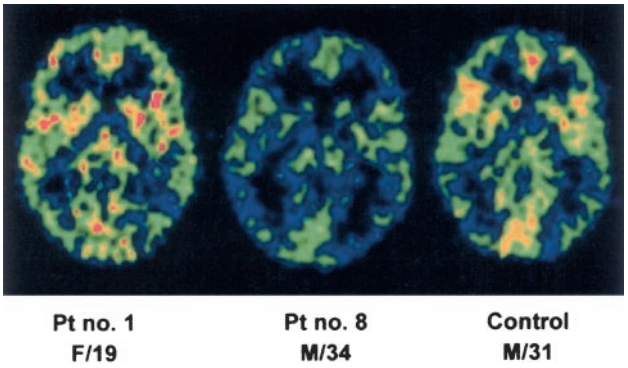

Figure 2. Representative PET scans of the CBF. In the youngest CADASIL patient (patient 1, left) without strokes and infarcts, the CBF in the WM is comparable to that in a control person (right); however, in the cerebral cortex it is somewhat higher. In patient 8 (middle) with 1 stroke and 9 lacunar infarcts in his T1w MRI, the CBF is clearly lower than in the control.

To reduce interindividual nondisease-dependent variation in CBF values, the percentage of CBF in frontal WM of that in frontal cortex was calculated in each individual. The mean percentages differed significantly ($P<0.001$) between the CADASIL and control groups (29.2% versus 38.1%).

Regional Glucose Metabolism Rates

In the CADASIL patients, the age-adjusted mean $rCMR_{gluc}$ values in all brain regions were lower, but not significantly, than in the controls (Table 3). The patients' $rCMR_{gluc}$ values decreased with age (data not shown). In the patients, the CBF and $rCMR_{gluc}$ values correlated significantly with each other in all examined GM regions, but not in WM.

Magnetic Resonance Imaging

All patients, including the youngest (19-year-old woman), had MRI findings (ranging from 4 to 41 according to Scheltens rating scale;[20] Table 1). Infarcts were detected in T1w images in all but the 4 youngest patients. The MRI scores increased with age ($r=0.69$, $P=0.007$). The average CBF values correlated inversely with Scheltens scores: in the frontal WM (regional: $r=-0.63$, $P=0.02$; and sum score: $r=-0.54$, $P=0.05$), in the occipital WM (regional: $r=-0.58$, $P=0.03$; and sum score: $r=-0.79$, $P=0.001$), and in the putamen (regional: $r=-0.79$, $P=0.001$; and sum score: $r=-0.81$, $P<0.001$). The $rCMR_{gluc}$ values did not correlate with Scheltens scores except in the putamen (regional: $r=-0.82$, $P<0.001$; sum score: $r=-0.83$, $P<0.001$).

Discussion

Our results demonstrate that CBF in WM is decreased in third decade of life, when T2w MRI changes appear and silent cerebral infarcts are possible but the patients have not experienced strokes. Total CBF (measured by phase contrast MRI in basilar and internal carotid arteries) was recently shown to be reduced in CADASIL patients in their late 20s.[21] In WM, reductions of parenchymal CBF have been reported in later adulthood.[7,8,10] In MRI, the changes appear to become detectable slightly earlier than in PET, but the small number of patients and great interindividual variation in CBF preclude a definite conclusion. In general, the reduction of CBF in WM and the increase of T2w MRI changes seem to appear in parallel. In our study, rCMRgluc was lower in the patients than in the controls, similar to those reported in cerebral cortex in midlife and late adulthood.[9]

In patients younger than 30 years without stroke and with low MRI score, CBF in WM was already slightly lower than in the controls. Unexpectedly, the mean cortical CBF in patients younger than 30 years was higher than in the controls, but in older patients it decreased below the mean level of the controls, but never to such an extent as the WM CBF (Table 2, Figure 1). Similarly, in a bolus-tracking MRI study, cortical CBF in patients older than age 40 years was only slightly lower than in the controls.[10] The increased

TABLE 3. $rCMR_{gluc}$ Values ($\mu mol \cdot mL^{-1} \cdot min^{-1}$) in Regions of Interest in Patients and Controls

		Cerebral Cortex						White Matter	
	Age (y)	Frontal	Sensorimotor	Temporal	Hippocampus	Putamen	Cerebellum	Frontal	Occipital
Patient average	32.8	0.41	0.39	0.36	0.23	0.39	0.31	0.15	0.14
SD	6.7	0.07	0.05	0.05	0.04	0.07	0.05	0.02	0.02
Control average	45.3	0.42	0.40	0.39	0.26	0.45	0.33	0.18	0.17
SD	10.4	0.06	0.06	0.06	0.04	0.08	0.05	0.03	0.04

cortical CBF in younger CADASIL patients and its marked decrease in older patients cannot be explained by aging alone. The average annual overall decrease in normal GM is reported to be only 0.37%,[22] whereas in our patients' frontal cortex it was ≈2.5% per year. It could be hypothesized that at an early stage, CBF via the deep penetrating arteries to the WM is reduced to such an extent that WM ischemia induces compensatory dilatation of cortical arteries, whereas the more severely affected WM arteries cannot dilate. At later stages, the cortical arteries also become affected and can no longer react by hyperemia. In accordance with this view, acetazolamide was reported to increase CBF less in T2w hyperintense WM than in the cortex.[10]

The exact cause of the reduced CBF in WM at the very early stage in young adults is unknown. At a corresponding age, retinal electrophysiological disturbances related to blood supply have been reported.[23] Remarkably, the accumulation of granular osmiophilic material and degeneration of vascular smooth muscle cells begin before age 20,[2] and most likely these structural changes have a causal relationship with the CBF reduction. Alternatively, arteries in CADASIL patients may be developmentally altered, because *Notch* family genes are involved in angiogenesis.[24]

Not much is known about $rCMR_{gluc}$ in WM. Thus, we can only speculate why in our young CADASIL patients that $rCMR_{gluc}$ in WM remained at a relatively normal level. It appears that the uptake of glucose from blood is sufficient or maybe even increased at reduced CBF levels. The trend of lower $rCMR_{gluc}$ in our young adults agrees with the recent report on cognitively and functionally impaired elderly CADASIL patients, in whom cortical $rCMR_{gluc}$ was significantly lower than in the 20-years–younger controls in that study.[9]

In conclusion, in CADASIL there is an early significant decrease in CBF and an impaired rCMRgluc in WM, which is in accordance with the predominant affect of deep penetrating arteries. The parallel appearance of CBF reduction and MRI changes in WM implies early tissue damage in CADASIL.

Acknowledgments

This study has been supported by research grants from the Academy of Finland, project 50046, Sigrid Juselius Foundation, EVO research Funds of Turku University Hospital, Turku University Foundation, Neurology Foundation, Finnish Cultural Foundation, Gamla Tjänarinnor Foundation, Gun and Bertil Stohne's Foundation. We are grateful to Tero Wahlberg, MSci for performing the statistical analyses and to Kaarina Amberla, MSci and Minna K. Wäljas, MSci for performing the neuropsychological tests. The assistance of the staff of the Turku PET Centre is thankfully acknowledged.

References

1. Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, Alamowitch S, Domenga V, Cecillion M, Marechal E, Maciazek J, Vayssiere C, Cruaud C, Cabanis EA, Ruchoux MM, Weissenbach J, Bach JF, Bousser MG, Tournier-Lasserve E. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature.* 1996;383:707–710.
2. Kalimo H, Ruchoux MM, Viitanen M, Kalaria RN. CADASIL: a common form of hereditary arteriopathy causing brain infarcts and dementia. *Brain Pathol.* 2002;12:371–384.
3. Chabriat H, Vahedi K, Iba-Zizen MT, Joutel A, Nibbio A, Nagy TG, Krebs MO, Julien J, Dubois B, Ducrocq X, Levasseur M, Homeyer P, Mas JL, Lyon-Caen O, Tournier Lasserve E and Bousser MG. Clinical spectrum of CADASIL: a study of 7 families. *Lancet.* 1995;346:934–939.
4. Dichgans M, Mayer M, Uttner I, Bruning R, Muller-Hocker J, Rungger G, Ebke M, Klockgether T, Gasser T. The phenotypic spectrum of CADASIL: clinical findings in 102 cases. *Ann Neurol.* 1998;44:731–739.
5. Chabriat H, Levy C, Taillia H, Iba-Zizen MT, Vahedi K, Joutel A, Tournier-Lasserve E, Bousser MG. Patterns of MRI lesions in CADASIL. *Neurology.* 1998;51:452–457.
6. Yousry TA, Seelos K, Mayer M, Bruning R, Uttner I, Dichgans M, Mammi S, Straube A, Mai N, Filippi M. Characteristic MR lesion pattern and correlation of T1 and T2 lesion volume with neurologic and neuropsychological findings in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). *Am J Neuroradiol.* 1999;20:91–100.
7. Tuominen S, Juvonen V, Amberla K, Jolma T, Rinne JO, Tuisku S, Kurki T, Marttila R, Poyhonen M, Savontaus ML, Viitanen M, Kalimo H. Phenotype of a homozygous CADASIL patient in comparison to 9 age-matched heterozygous patients with the same R133C Notch3 mutation. *Stroke.* 2001;32:1767–1774.
8. Chabriat H, Bousser MG, Pappata S. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: a positron emission tomography study in two affected family members. *Stroke.* 1995;26:1729–1730.
9. Tatsch K, Koch W, Linke R, Poepperl G, Peters N, Holtmannspoetter M, Dichgans M. Cortical hypometabolism and crossed cerebellar diaschisis suggest subcortically induced disconnection in CADASIL: an ^{18}F-FDG PET study. *J Nucl Med.* 2003;44:862–869.
10. Chabriat H, Pappata S, Ostergaard L, Clark CA, Pachot-Clouard M, Vahedi K, Jobert A, Le Bihan D, Bousser MG. Cerebral hemodynamics in CADASIL before and after acetazolamide challenge assessed with MRI bolus tracking. *Stroke.* 2000;31:1904–1912.
11. Bruening R, Dichgans M, Berchtenbreiter C, Yousry T, Seelos KC, Wu RH, Mayer M, Brix G, Reiser M. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: decrease in regional cerebral blood volume in hyperintense subcortical lesions inversely correlates with disability and cognitive performance. *Am J Neuroradiol.* 2001;22:1268–1274.
12. de Haan R, Limburg M, Bossuyt P, van der Meulen J, Aaronson N. The clinical meaning of Rankin "handicap" grades after stroke. *Stroke.* 1995; 26:2027–2030.
13. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189–198.
14. Sipilä HT, Clark JC, Peltola O. An automatic $H_2{}^{15}O$ production system for heart and brain studies. *J Labelled Comp Radiopharm.* 2001;44(suppl): S1066–S1068.
15. Raichle ME, Martin WR, Herscovitch P, Mintun MA, Markham J. Brain blood flow measured with intravenous $H_2{}^{15}O$. II. Implementation and validation. *J Nucl Med.* 1983;24:790–798.
16. Hamacher K, Coenen HH, Stöclin G. Efficient stereospecific synthesis of no-carrier- added 2-[^{18}F]-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. *J Nucl Med.* 1986;27:235–238.
17. Solin O, Bergman J, Haaparanta M, Reissell A. Production of ^{18}F from water targets. Specific radioactivity and anionic contaminants. *Int Radiat Isot.* 1986;34:1065–1071.
18. Pellizari CA, Chen GTY, Spelbring DR, Weichselbaum RR, Chen CT. Accurate three-dimensional registration of CT, PET and/or MR images of the brain. *J Comput Assist Tomogr.* 1989;13:20–26.
19. Patlak CS, Blasberg RG. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations. *J Cereb Blood Flow Metab.* 1985;5:584–590.
20. Scheltens P, Barkhof F, Valk J, Algra PR, van der Hoop RG, Nauta J, Wolters EC. WM lesions on magnetic resonance imaging in clinically diagnosed Alzheimer's disease. *Brain.* 1992;115:735–748.
21. van den Boom R, Lesnik Oberstein SA, Spilt A, Behloul F, Ferrari MD, Haan J, Westendorp RG, van Buchem MA. Cerebral hemodynamics and white matter hyperintensities in CADASIL. *J Cereb Blood Flow Metab.* 2003;23:599–604.
22. Bentourkia M, Bol A, Ivanoiu A, Labar D, Sibomana M, Coppens A, Michel C, Cosnard G, De Volder AG. Comparison of regional cerebral blood flow and glucose metabolism in the normal brain: effect of aging. *J Neurol Sci.* 2000;181:19–28.
23. Parisi V, Pierelli F, Fattapposta F, Bianco F, Parisi L, Restuccia R, Malandrini A, Ferrari M, Carrera P. Early visual function impairment in CADASIL. *Neurology.* 2003;60:2008–2010.
24. Gridley T. Notch signaling during vascular development. *Proc Natl Acad Sci.* 2001;98:5377–5378.