Cerebral hemodynamics and white mater hyperintensities in CADASIL

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Abstract
In cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) no correlation has been found between white matter hyperintensities (WMH) and cerebral blood flow (CBF) changes. We conducted an MRI study of 40 CADASIL patients (mean age 46±11, range 21-59 years) and 31 volunteers (mean age 43±12 years, range 22-67 years), and we assessed in both groups CBF and WMH load. In CADASIL patients we found a significant correlation between the amount of WMH and a decrease in flow. These observations suggest that CBF changes in CADASIL patients relate directly to the production of WMH.

Introduction
CADASIL is a small-artery disease caused by mutations in the Notch3 gene on chromosome 19, leading to migraine, transient ischemic attacks and early onset of lacunar stroke with dementia[1,2]. A hallmark of CADASIL is the presence of diffuse WMH predominating in the subcortical areas, often associated with small infarcts within the white matter and basal ganglia[3]. Pathological examination of small and medium sized leptomeningeal and long perforating arteries reveals degeneration of smooth muscle cells and thickening of the media[4].

It has been shown that diminished CBF and/or cerebrovascular reactivity (CVR) and cerebral WMH coexist in elderly patients without CADASIL[5]. Also in CADASIL coexistence of reduced CBF and WMH has been found[6-9]. However, in CADASIL and in normal aging, the relation between WMH and flow changes is not clear.

The aim of the present study was to establish the relation between WMH and cerebral flow changes in CADASIL patients.

Materials and methods
We performed flow measurements in 40 patients (mean age 46±11, range 21-59 years) with DNA proven CADASIL. Thirty-one volunteers (mean age 43±12 years, range 22-67 years), without a history of cardiovascular events served as a control group. Twenty-three CADASIL patients and 23 control subjects gave permission for the administration of acetazolamide (ACZ).

All imaging was performed on a 1.5T MR system (Philips Medical Systems, Best, The Netherlands). For flow measurements we used a non-triggered gradient echo phase contrast technique (TR/TE 16/9ms; flip angle 7.5°; 5 mm slice thickness; FOV 250 x 188 mm). The scans were performed in a plane perpendicular to the left and right internal carotid artery and the basilar artery. CBF was measured 10 minutes before the administration of 14 mg/kg ACZ intravenously and repeated at 5, 10, 15, and 20 minutes after the administration of ACZ.

Images were analysed using the locally developed software package FLOW® (Department of Radiology; Division of Imaging Processing, LUMC). Flow in the basilar artery and the left and right internal carotid artery were added and considered to represent the total cerebral blood flow (TCBF) in ml/min to the brain. The baseline TCBF (bTCBF) and the maximum TCBF (mTCBF) were respectively defined as TCBF before and the maximum TCBF obtained after the administration of ACZ. CVR was defined as percentage increase in TCBF occurring during the administration of ACZ.

White matter lesions were rated from hard copies of proton density and T2 weighted axial images by one neuroradiologist (MvB) blind to the diagnosis, using a validated visual scoring system[10].

Results
In the CADASIL population the WMH load increased with increasing age, which was not found in control subjects. In both groups, all 3 flow parameters diminished as a function of age. In the group of CADASIL patients, the 3 flow parameters were lower then in the control group (data not shown).

The results for flow parameters are given in table 1. In both groups, the average TCBF increased significantly after the administration of ACZ ($p<0.01$). In CADASIL, bTCBF and mTCBF were significantly decreased ($p<<0.01$) as compared to the control values (566 vs. 699 ml/min and 930 vs. 1155 ml/min respectively). No significant difference of CVR (62% vs. 69%) was found between the two groups.

Table 1. Average bTCBF, mTCBF and CVR in patients and volunteers.

	N	bTCBF in ml/min (±SD)	N	mTCBF in ml/min (±SD)	CVR in % (±SD)
CADASIL	40	**566** (±133)	23	**930** (±233)	62 (±18)
Volunteers	31	**699** (±141)	23	**1155** (±258)	69 (±19)

Bold: significant difference ($p<0.05$) between CADASIL and volunteers.

Because no increase in the amount of WMH during ageing was present in the control group, we did not perform a correction for age. In CADASIL patients there was a statistically significant inverse correlation between the amount of WMH and bTCBF and mTCBF (table 2).

Table 2. Pearson correlation coefficients for flow parameters versus white matter hyperintensities

	White matter hyperintensities	
flowparameters	*r*	P
bTCBF	-.47	0.002
mTCBF	-.48	0.020
CVR	-.36	0.097

Conclusion
In the present study we investigated hemodynamic flow parameters in CADASIL patients by using QF and related the outcome to the amount of WMH. We found a decrease in bTCBF and mTCBF in CADASIL patients. Furthermore, we found a significant correlation between WMH load and a decrease in CBF. These observations suggest that WMH in CADASIL patients are the result of a decreased flow due to arteriopathy.

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