Cerebral vasoreactivity as the main determinant of progression of white matter hyperintensities in small vessel disease: CADASIL as a monogenetic model

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Background and purpose: Cerebral small vessel disease is characterized by white matter hyperintensities (WMHs) and lacunar infarcts on MRI and can lead to stroke and dementia. Although the pathophysiological basis of small vessel disease has yet to be elucidated, an important role for basal total cerebral blood flow (TCBF) and cerebral vasoreactivity (CVR) has been assumed. Studies performed in the general population were mostly cross sectional and have been unable to demonstrate a causal relation. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), which is caused by *NOTCH3* mutations, is a unique monogenetic model to study the pathophysiology of arterial small vessel disease. The aim of this study is to longitudinally investigate the role of TCBF and CVR on the progression of MRI abnormalities in CADASIL, to get more insight into the pathophysiology of small vessel disease in general.

Methods: Twenty-five *NOTCH3* mutation carriers and 13 controls were examined using a uniform MRI protocol on the same 1.5T MR system at baseline and follow-up MRI at baseline and after 7 years of follow-up. The number of lacunar infarcts and microbleeds were counted manually. WMH volume was measured using semi-automated segmentation software, and expressed as percentage of total brain parenchymal volume. Basal TCBF (n=25) and CVR (n=14) were measured with a gradient-echo phase-contrast technique before and after administration of intravenous acetazolamide. Finally, we performed MR angiography of the neck vessels to rule out concomitant large vessel disease.

Results: At baseline, mutation carriers had significantly lower TCBF values (p=0.003) than controls, whereas CVR was identical between the two groups. Mutation carriers had significantly more WMHs and lacunar infarcts than controls, whereas the difference in microbleeds was not significant. At follow-up, all MRI abnormalities in mutation carriers had increased significantly. Low TCBF was not associated with faster progression of MRI abnormalities. However, patients with low CVR values demonstrated a significantly larger increase in WMH volume than patients with high CVR values ($p < 0.001$). CVR was not associated with progression of neither lacunar infarcts nor microbleeds.

Conclusions: This study provides support that impaired CVR is an important causal factor in development of WMHs in CADASIL. Since CADASIL is a monogenetic model of small vessel disease, this new insight may also be valid for the pathophysiology of small vessel disease in general. Longitudinal studies in the general population should be performed to confirm this suggestion.

Table 1: Associations between baseline flow characteristics and 7 year progression of MRI abnormalities in *NOTCH3* mutation carriers

	Low TCBF (n=12)	High TCBF (n=13)	Low CVR (n=7)	High CVR (n=7)
Δ White Matter Hyperintensities (%, SD)	2.8 (2.7)	2.0 (1.6)	2.9 (1.5)	0.37 (0.03)***
Δ Infarcts (median, range)	1 (0-11)	2 (0-21)	2 (0-21)	0 (0-3)
Δ Microbleeds (median, range)	0 (0-21)	0 (0-4)	0 (0-4)	0 (0-4)

Student t test used for WMHs. Mann Whitney U test for infarcts and microbleeds
*** = difference ($p<0.001$) between high and low
TCBF = baseline total cerebral blood flow; CVR = baseline cerebrovascular reactivity