Coronary microvascular function is impaired in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL; OMIM 125310) is a rare inherited disease, caused by NOTCH3 gene mutations. Main clinical manifestations of CADASIL include recurrent subcortical ischemic events, migraine, cognitive impairment and psychiatric disturbances. CADASIL is a systemic microangiopathy and cardiac involvement has been observed in a series of Dutch patients, presenting higher frequency of myocardial infarction compared to non-mutated relatives and general population. In particular, electron microscopic examination of myocardial tissue of a study participant demonstrated CADASIL characteristics.

We sought to investigate the relationship between CADASIL and microvascular dysfunction (MVD).

Seventeen patients with genetically-confirmed CADASIL, aged <60 years, with ≤ 1 cardiovascular risk factor (current smoke, diabetes, hypertension, dyslipidemia), recent (<3 months) neurological evaluation with neuropsychological tests and 3 Tesla brain magnetic resonance imaging (MRI) underwent 12-lead ECG, echocardiography, and measurement of maximal myocardial blood flow following Regadenoson infusion (Reg-MBF) by 13NH3positron emission tomography (PET), to investigate the presence of coronary microvascular dysfunction (CMD). Coronary flow reserve (CFR) was defined as Reg-MBF/resting MBF. PET results were compared to those of 15 healthy controls matched for age and sex recruited among a historical cohort of healthy patients. The study was approved by the institutional review board and all the subjects gave informed consent.

Mean age was 40±9 years (range 28–57 years); 6 patients (35%) were male. One was a current smoker and 3 ex-smokers; 1 patient was on aspirin, 1 on acetazolamide and 2 on escitalopram, none was taking statins. 12 patients (71%) presented with migraine, 9 (53%) had psychiatric disturbances and 1 (6%) had a previous stroke. Brain MRI showed mild-moderate and severe leukoencephalopathy in 11 (65%) and 5 (29%) patients respectively, lacunes were present in 14 patients and microbleeds in 1; one patient had normal findings. Both Reg-MBF and CFR were blunted in CADASIL patients compared with controls (Reg-MBF 2.46±0.54 versus 3.09±0.44 ml/gr/min respectively, $p<0.001$; CFR 2.74±0.36 vs. 3.28±0.66, respectively, $p<0.01$). In 3 male patients (17%), CFR reduction was severe (<2). Segmental Reg-MBF analysis of left ventricular flow showed diffuse hypoperfusion, excluding preferential regional involvement. No correlations were found between Reg-MBF values and neuropsychological performance or cerebral lesion burden, suggesting that neurological and cardiac involvement might be independent in CADASIL.

These data represent the first documentation of coronary microvascular involvement in a group of young and mildly symptomatic CADASIL patients, confirming the systemic nature of the disease. This proof of concept study expands our understanding of genetically-driven CMD.

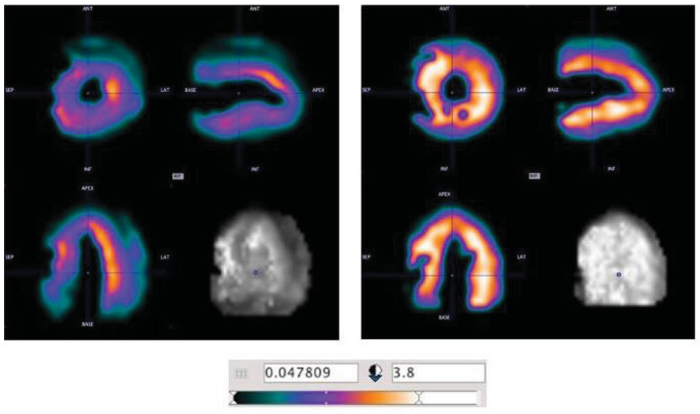

Figure. Myocardial perfusion $^{13}NH_3$ positron emission tomography (PET). Left panel shows reduced maximum myocardial blood flow in a CADASIL patient after Regadenoson infusion (Reg-MBF) (minimum Reg-MBF 0.99 ml/min/g in anterobasal region, maximum 2.28 ml/min/g in inferoseptal region, global Reg-MBF 1.77 ml/mg/min) in comparison with a healthy control (right panel). The parametric maps show maximal myocardial blood flow following Regadenoson infusion in mL/min/g according to the scale below.