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Plasma Levels of Asymmetric Dimethylarginine in Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarct and Leukoencephalopathy

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Key Words
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy · Genetic ischemic stroke · Nitric oxide synthase inhibitor · Asymmetric dimethylarginine

Abstract
Background: Asymmetric dimethylarginine (ADMA) is a marker of endothelial dysfunction and a new independent risk factor for adverse cerebrovascular events in small vessel disease. Conversely, L-arginine (LARG) may have a protective role. ***Methods:*** To assess ADMA, LARG levels and LARG/ADMA ratio in 16 patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and normal controls, and to look for possible correlations with white matter changes. Plasma levels of ADMA and LARG were assayed by high-performance liquid chromatography in all subjects. The overall T_1 and T_2 lesion load was obtained from brain MRI of patients with CADASIL. ***Results:*** ADMA plasma concentrations (1.5 ± 2.0 μM) were significantly higher ($p < 0.05$) in CADASIL patients than in controls (0.35 ± 0.075 μM). Analyzing only CADASIL subjects, an inverse borderline-significant correlation was found between LARG/ADMA (190 ± 20) and T_2-weighted lesion volumes (57.9 ± 46.5; $r = -0.578$, $p = 0.024$). ***Conclusion:*** Our results may indicate the possible coexistence of endothelial dysfunction in CADASIL patients, broadening the range of potentially pathogenetic mechanisms in this disease and providing insights for future therapeutic strategies.

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited form of small vessel disease due to mutations in the *Notch3* gene [1] associated with repeated strokes, dementia and MRI evidence of lacunar infarcts and leukoaraiosis [2].

Although smooth muscle cells of the media are targeted by *Notch3* mutations, their role in the pathogenesis of arteriolar dysfunction has not been completely clarified and other factors need to be investigated in more detail [3]. Among these, endothelial changes, reported in previous pathological studies, might contribute to vessel damage [4, 5].

Emerging evidence indicates that endothelial dysfunction, resulting from impaired bioavailability of nitric oxide (NO), plays a pivotal role in the atherothrombotic process. Endothelial-derived NO production is reduced

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