Increased QT variability in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

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Background and purpose: Although sudden death (SD) accounts for numerous cases of premature mortality in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), the risk factors responsible for this dramatic event remain unclear. We sought possible differences in the QT variability index (QTVI) – a well-known index of temporal dispersion in myocardial repolarization strongly associated with the risk of SD – between a group of patients with CADASIL and healthy controls. *Methods:* A total of 13 patients with CADASIL and 13 healthy volunteers underwent a 5-min electrocardiogram recording to calculate the QTVI. All the patients also underwent a clinical assessment, including functional status by Rankin score, and a magnetic resonance imaging (MRI) brain scan for quantitative analysis of T2-weighted (T2-W) and T1-weighted (T1-W) lesion volume (LV). *Results:* Short-term QT-interval analysis showed significantly higher QTVI ($P = 0.029$) in patients than in controls. In patients, notwithstanding the limitations of the small sample size, QTVI also well correlated with T1-W LV ($r = 0.747$, $P = 0.003$) and T2-W LV ($r = 0.731$, $P = 0.005$). *Conclusion:* Because patients with CADASIL have increased temporal cardiac repolarization variability as assessed by QTVI, this mechanism could underlie these patients' risk of SD. Whether this easily assessed, non-invasive marker could be used to stratify the risk of malignant ventricular arrhythmias in patients with CADASIL and, possibly, to guide their therapeutic management warrants confirmation from larger prospective studies.

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited and generalized small- and medium-sized arteriopathy caused by highly stereotyped mutations in the *Notch*3 gene [1]. Clinical manifestations of the disease are usually confined to the central nervous system and include recurrent strokes, migraine with aura, mood disturbances and cognitive impairment [2]. Patients with CADASIL have a highly variable clinical course [3] with a notable incidence of sudden death (SD) [4]. SD may be caused by a number of factors, including cardiac arrhythmias and myocardial infarctions. This dramatic event is usually accompanied by increased sympathetic modulation with low heart rate variability (HRV) [5,6] or by augmented temporal dispersion in myocardial repolarization with an increase in the various indices of QT variability [7–9], or both. Some investigators tried to strengthen the predictive value of HRV and QT variability derived indices by normalizing them through the QT variability index (QTVI) [9,10] and demonstrated that this index tends to increase in various populations at high risk of SD [10–14].

A recent study conducted in patients with CADASIL, found a significant reduction in all frequency domain measures of HRV, indicating an autonomic derangement thus possibly explaining in part their high risk of SD [15]. To our knowledge, no study has investigated whether temporal QT dispersion is increased in patients with CADASIL. Having this information could be important to identify patients in whom the typical CADASIL-induced changes in coronary vessels could increase the risk of malignant arrhythmias [16–18].

In this preliminary study, we sought possible differences in the QTVI – a well-known index of temporal

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