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Silent Small-Vessel Cerebrovascular Disease and Silent Myocardial Ischemia in Families with Premature Coronary Disease

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Cerebrovascular disease and coronary artery disease (CAD) co-occur, aggregate in families, have a silent atherogenic period and share risk factors [1, 2]. The presence of brain white matter hyperintensities (WMH) strongly suggests small-vessel cerebrovascular disease (SVCD) [3]. Exercise-induced myocardial ischemia in the absence of coronary lesions suggests early coronary atherosclerosis [4]. We determined the prevalence of silent SVCD, compared it with a reference cohort in the Atherosclerosis Risk in Communities (ARIC) study [5] and determined the association of SVCD with silent exercise-induced myocardial ischemia in healthy siblings of probands with

CAD <60 years of age. Siblings with known clinical vascular disease and diabetes were excluded.

The siblings underwent brain magnetic resonance imaging to identify WMH using the published criteria of the ARIC study [5], and a maximal exercise test with thallium-201 single-photon emission tomography of the heart with rest and reperfusion imaging. Exercise-induced ischemia was defined as a reversible segmental perfusion defect as per standard protocols [6].

The participants were 51% female, 24% African American, 6.7% had diabetes, and 16% smoked cigarettes. The prevalence of SVCD was 69%. Sibs with SVCD compared to those without SVCD were significantly older (62 ± 9 vs. 48 ± 9 years, $p < 0.0001$), had higher glucose levels (100 ± 21 vs. 87 ± 10 mg/dl, $p = 0.01$) and were more likely to be hypertensive (48 vs. 20%, $p = 0.05$). The ARIC cohort was 59.6% female, older (mean age = 62.6 ± 4.3 years), with more African Americans (49%), a similar percentage of smokers (17.9%) and a higher prevalence of hypertension (49.2%) [5]. The CAD, stroke and diabetes prevalence in ARIC was 5.8, 1.5 and 15% respectively, compared to none in siblings.

A significantly higher odds ratios for WMH lesions was noted in siblings compared to ARIC within the same age groups and in the younger sibling age group (table 1).

Table 1. Prevalence of SVCD by age group in siblings compared to the ARIC population

	SVCD prevalence, % (n)	p value	Odds ratios [95% CI]
ARIC ages 55–72 years (n = 1,890)	15.3 (290)	reference	reference
Sibs ages 55–72 years (n = 25)	80 (20)	<0.001	22.07 [8.21–59.27]
Sibs ages 35–54 years (n = 20)	55 (11)	<0.001	6.74 [2.77–16.42]

p value: Fisher's exact test for prevalence in siblings by age group compared to ARIC subjects. Odds ratios: unadjusted odds ratios in siblings by age group compared to ARIC subjects (the ratio of the odds of SVCD in sibs to the odds SVCD in ARIC).

Exercise-induced silent myocardial ischemia occurred in 20% of the siblings. Of the 9 siblings with exercise-induced myocardial ischemia, 88.8% (n = 8) also had SVCD, while of the 36 persons without silent CAD, 66.7% had SVCD (p = 0.19).

Healthy siblings from families with premature CAD had an SVCD prevalence similar to older subjects with a greater risk factor burden in ARIC. Silent myocardial ischemia was almost always associated with silent SVCD in siblings, demonstrating early preclinical disease in both vascular beds that may share a similar biology. Although it is not yet established whether the myocardial-infarction-associated polymorphisms on chromosome 9p21 are related to ischemic stroke in general or only large-artery ischemic stroke, ischemic disease events in the brain and heart have shown at least one common genetic locus [7]. This suggests that high-risk families may yield insight into preclinical atherogenic vascular disease mechanisms and genetic susceptibility.

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