Neuroepidemiology 2017;49:62–63
DOI: 10.1159/000480238**White Matter Lesion Progression and Cognitive Function Over 5 Years in a Young Susceptible Population**

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Cerebrovascular disease and attendant vascular risk factors cluster in families of patients with early-onset coronary artery disease [1]. In a prior cross-sectional study of 563 cognitively normal middle-aged relatives, we found a high prevalence of early white matter hyperintensity lesions (WMHL) [1–3], and further ob-

served lower cognitive function scores among those with higher WMHL volumes [4]. Most prior WMHL studies have occurred in the elderly or in populations with dementia [5]. The extent to which WMHL progression and decline in cognitive function occur in a quiescent preclinical state in healthy middle-aged persons remains unknown [6, 7]. We determined the progression of silent WMHL and changes in cognitive function over 5 years in a random sample of 20 healthy relatives (aged 50–59) years of patients with coronary artery disease <60 years of age (one subject per family). Persons with any serious physical or psychiatric morbidity, neurological disease, cardiovascular disease, and diabetes were excluded.

At baseline and follow-up, subjects underwent 3-Tesla brain magnetic resonance imaging; WMHL volumes were determined using T1-weighted images acquired using MPRAGE [8]. All volumes were measured with an automated standard pipeline as described previously [3]. Cognitive function was measured using standard tests [4], and traditional vascular risk factors were assessed. Changes over 5 years are presented in Table 1. Changes in WML volumes and in cognition from baseline to follow-up were each compared with paired *t* tests. The prevalence of WMHL was 92% at baseline and the overall progression was significant; for men, *p* = 0.006, for women, *p* = 0.062, for African Americans, *p* = 0.019, and European Americans, *p* = 0.018. Of 20 persons, 19 had increased WMHL volume. Decline was observed in all cognitive function tests in all races and gender groups; 13 persons (65%) had worse cognitive performance on 4 or more of the tests at follow-up. For the Grooved Pegboard Test, the scores went up reflecting generally worse performance. Vascular risk factors were prevalent at both baseline and follow-up and did not change. In simple bivariable analyses, no risk factors were associated with WMHL change.

These striking findings are among the first to demonstrate significant quantitative WMHL volume progression and cognitive decline in a healthy middle-aged population over just 5 years, both in African Americans and European Americans, and in both genders. This small pilot study suggests that quiescent brain white matter lesion progression can be detected early, accompanied by significant but mild multidimensional cognitive decline in a healthy susceptible population using state-of-the-art quantitative volumetric imaging techniques. Further studies of this type including younger and middle-aged healthy populations may better define biological processes causing white matter lesion progression and offer opportunities to ameliorate associated serious cognitive decline at later ages.

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Table 1. GeneSTAR WMHL progression and cognitive function changes overall (*n* = 20)

WMHL on MRI	mean (SD)	<i>p</i> value***
WMHL volume mm ³ , baseline	2,077 (1,935)	NA
WMHL volume mm ³ , follow-up	2,896 (2,654)	NA
Overall change, mm ³	819 (914)	0.0008
Cognitive function* tests		
Mini-Mental State Examination change	–1.15 (1.57)	0.0039
Delayed recall-short change	–1.15 (1.53)	0.0033
Delayed recall-long change	–2.05 (1.82)	<0.0001
Digit symbol substitution change	–3.90 (6.53)	0.0151
Verbal fluency change	–1.95 (5.33)	0.1180
Digit span change	–1.00 (2.29)	0.0662
Grooved pegboard test** change	3.03 (10.9)	0.2312
Demographics and comorbidity at follow-up		
Age, years, mean (SD)	54.1 (3.5)	NA
Education, years, mean (SD)	13.7 (3.0)	NA
% Hypertensive	45	NA
% Smoking	15	NA
% Obese	50	NA
% Male	55	NA
% African American, % European American	45; 55	NA

* Cognitive function tests: minus score represents worse performance.

** Grooved pegboard test: plus score represents worse performance.

*** *p* values from paired *t* tests.

NA, Non-applicable.

References

- 1 Nyquist PA, Wityk R, Yanek LR, et al: Silent small-vessel cerebrovascular disease and silent myocardial ischemia in families with premature coronary disease. *Neuroepidemiology* 2009;33:66–67.
- 2 Nyquist PA, Bilgel M, Gottesman R, et al: Age differences in periventricular and deep white matter lesions. *Neurobiol Aging* 2015;36:1653–1658.
- 3 Nyquist PA, Bilgel MS, Gottesman R, et al: Extreme deep white matter hyperintensity volumes are associated with African American race. *Cerebrovasc Dis* 2014;37:244–250.
- 4 Nyquist PA, Yanek LR, Bilgel M, et al: Effect of white matter lesions on manual dexterity in healthy middle-aged persons. *Neurology* 2015;84:1920–1926.
- 5 Longstreth WT Jr, Manolio TA, Arnold A, et al: Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke* 1996;27:1274–1282.
- 6 Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM: Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med* 2003;348:1215–1222.
- 7 Wardlaw JM, Valdes Hernandez MC, Munoz-Maniega S: What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. *J Am Heart Assoc* 2015;4:001140.
- 8 Bazin PL, Cuzzocreo JL, Yassa MA, et al: Volumetric neuroimage analysis extensions for the MIPAV software package. *J Neurosci Methods* 2007;165:111–121.