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White matter grade and ventricular volume on brain MRI as markers of longevity in the cardiovascular health study

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Abstract

High white matter grade (WMG) on magnetic resonance imaging (MRI) is a risk factor for dementia, stroke and disability. Higher ventricular size is a marker of brain "atrophy." In the Cardiovascular Health Study (CHS) ($n = 3245$) mean age 75 years, 50% black and 40% men, we evaluated WM and ventricular grade (VG), total, cardiovascular and noncardiovascular mortality and longevity before and after adjusting for numerous determinants of longevity over an approximate 10–12 years of follow-up. A low WMG and VG was a marker for low total, cardiovascular and noncardiovascular mortality and for increased longevity over 10+ years of follow-up. We estimated that a 75-year-old with WMG below median would have about a 5–6 years greater longevity and for VG about 3 years, than above the median even after adjustment for numerous risk factors. Low WMG and VG on MRI is a powerful determinant of long-term survival among older individuals.

Keywords: MRI; White matter; Ventricular size; Survival; Aging; Cardiovascular disease

1. Introduction

The identification of objective markers of longevity among older individuals is important for both the study of the determinants of longevity and identification of potential therapeutic agents. Epidemiological studies, including the Cardiovascular Health Study (CHS), have shown that high ventricular grade (VG) and white matter grade (WMG) on magnetic resonance imaging (MRI) of the brain were predictors of dementia, which is associated with increased mortality [2,57,16,24,25,54].

High WMG is likely related to small vessel vascular disease in the brain [37,43]. Risk factors for high WMG include age, higher systolic blood pressure (SBP), carotid intimal medial thickness, and lower forced expiratory volume in 1 s (FEV1) [33,19]. A strong and direct linear relationship with SBP and WMG has been demonstrated for both men and women [33]. Many clinical features have also been correlated with high WMG in CHS, especially impaired cognition and lower extremity function [33]. High WMG was also an independent predictor of the risk of stroke and

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dementia [24,23,20,56,4]. Risk factors for high VG included white race, male sex, age, higher WMG and retinopathy [30]. High VG has also been associated with poorer cognitive and physical function and increased risk of dementia [25,30]. Preliminary data from CHS have suggested a lower mortality rate in 5-year follow-up for persons with lower ventricular size or WMG [32,31]. Longer-term follow-up and the independence of the associations of high WMG and ventricular size with mortality have not been examined. The leukoaraiosis and disability in the elderly (LADIS) study is evaluating age-related white matter change as an independent predictor of transition to disability in 639 subjects. They are using the Fazakas scale to quantify white matter lesions [42,12].

In this report from the CHS we evaluated measures of ventricular volume and white matter grade based on magnetic resonance imaging among 3245 CHS participants age 65+, mean age 75, in 1992–1994 and subsequent total mortality and survivorship through 30 June 2002.

We have tested the hypothesis that lower ventricular and/or WMG is inversely associated with total mortality and directly related to survivorship, and that the association persists after adjustment for clinical or subclinical cardiovascular disease (CVD), hypertension, diabetes, apolipoprotein E_4 ($ApoE_4$) and other measures in the CHS which have been related to survivorship.

2. Methods

The CHS is the largest longitudinal cohort that included MRI of the brain and long-term follow-up [34]. The design of the CHS has been previously published [15]. The original study included 5201 adults age 65+ from four communities in the United States. Eligible participants were noninstitutionalized and were originally recruited from June 1989 to May 1990. In 1992, 687 additional predominately African-American participants were recruited and enrolled. Participants had annual visits which included updated medical history, assessments of cognitive and physical function, phlebotomy, and electrocardiograms. Medical records were obtained to document reported cardiovascular events, which were adjudicated by a committee [45,21,44].

In 1992–1994, all subjects were invited to have an MRI of the brain. Detailed descriptions of the MRI techniques and methods of analysis have been published [60,36,35,5]. The scanning protocol included sagittal T1-weighted localized images and axial spin-density and T2-wieghted images. MR imaging included a T1-weighted (500/20 [repetition time ms/echo time ms], one signal acquired), sagittal-localizing sequence with a 5-mm section thickness, no section gap, 24-cm field of view, and 128×256 matrix. Midline sagittal images were used to identify the anterior commissure–posterior commissure line along which all oblique axial images were aligned. Spin-echo spin-density weighted (3000/30, one-half or one signal acquired), spin-echo T2-weighted (3000/90, one-half or one signal acquired), and T1-weighted (500/20, one or two signals acquired) oblique axial images with a 5-mm section thickness, no intersection gap, 24-cm field of view, and 192×256 matrix were acquired from the vertex to the foramen magnum on 1.5-T (GE Medical Sstems, Milwaukee, Wis; Picker, Cleveland, Ohio) instruments at three sites or a 0.35-T (Toshiba American Medical Systems, Duluth, Ga) instrument at one site [6].

The resulting images were displayed simultaneously on four 1024×1024-pixel workstation monitors for evaluation by trained readers. Each study had a primary and a secondary interpretation rendered by a different reader blinded to any information except that the studies were from the CHS. All primary readers (including RNB, SWW, TJM) were board-certified radiologists with subspecialty neuroradiology fellowship training. The group of secondary readers included the same radiologists plus and experienced neuroimaging technologist. Each reader had completed an MRI-interpretation training course specifically designed for the CHS project and had met specified reader-reproducibility criteria. Interpretations of the images were recorded in a computerized database that included fields for lesion number, location, size, signal intensity and anatomic location [6].

All axial images had 5 mm thickness without intersplice gaps and no contrast was used. The MRIs for both the initial and black cohorts were done at the same time with exactly the same protocol.

Ventricles were estimated from the T1-weighted axial images. Ventricular grade in this paper refers to the size of the lateral ventricles and estimated by the radiologist. WMG refers to the reading of white matter hyperintensities by the radiologist. The overall size of the lateral ventricles was determined using a linear scale from 0 to 9 based on a referenced standard. Zero was considered to be slitlike ventricles and grade 9, very marked increase in ventricular volume. White matter changes were estimated by the total extent of periventricular and subcortical white matter signal abnormality on spin-density weighted axial images graded by successive increase from no changes or barely detectable changes (grades 0 and 1, respectively) to almost all white matter involved (grade 9) [60]. Most of the high WMGs were periventricular rather than subcortical [24]. A brain infarct by MRI was defined as an area of abnormal signal intensity >3 mm in size in a vascular distribution that noted mass effects and vascular distribution [60,6].

In the CHS, inter-reader and intrareader reproducibility of both VG and WMG within one grade were good. Intrareader agreement within 1 grade was 94% with a κ of 0.89 for ventricles and 96.9% for WMG with a κ of 0.96 [60].

There was a modest association of VG, $r = 0.24$, with inner table distance, a measure of brain size, but no association with WMG and inner table diameter.

Two hundred and twenty-seven participants had dementia at the time of the MRI in 1992–1993 and have been excluded from the analysis [25,34]. Diagnosis of dementia was based