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Assessing the brain as an end-organ of vascular disease

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Abstract

A spectrum of common illnesses that constitute risk factors for cardiovascular diseases is associated with both cognitive impairment and high population mortality. Many clinical trials are focused on the prevention of cardiovascular mortality, but cognitive impairment should now be regarded as a similarly important outcome.

Given that vascular risk factors injure both the brain and the heart, cognitive outcomes are a surprisingly uncommon focus of cardiovascular studies, particularly treatment trials. This limitation, however, has now been eloquently addressed in a study by O'Donnell and colleagues.¹

Alzheimer disease is the major cause of cognitive impairment among individuals aged 70 years,² but current evidence suggests that an individual's lifetime risk of cerebrovascular disease might be similar or even higher than that of Alzheimer disease.³ Moreover, these two conditions commonly occur concomitantly, and this combination of brain pathologies is the greatest determinant of whether elderly individuals develop dementia.⁴ Not all vascular brain injury, however, is clinically symptomatic. The extent of subtle brain injury, such as silent brain infarction, white matter hyper-intensities on MRI, and even brain atrophy, increases with age and with degree of vascular risk factors, such as hypertension, diabetes mellitus, smoking, and obesity. In the original and offspring cohorts of the Framingham Heart Study,⁵ age-related increases in blood pressure—a common risk factor for vascular disease—precede the development of coronary artery disease and stroke by a decade or more. However, brain atrophy and silent brain infarction are already present by the age of 50 years (Figure 1). Population-based (or community-based) associations are not sufficient to determine causality, but longitudinal studies in the same cohort showed that vascular risk factors are associated with cognitive decline and changes in brain structure, which are also associated with impaired cognition.⁶ Additionally, MRI detection of extensive white matter hyperintensities and clinically silent brain infarction is strongly associated with incident dementia, stroke, and even death.⁷ Vascular risk factors that are widely recognized to cause cardiovascular disease are, therefore, similarly associated with stroke, brain injury, cognitive impairment, dementia, and death.

Competing interests

The author declares no competing interests.

In their study, O'Donnell and colleagues¹ examined whether a relationship exists between a common test of cognition—the mini-mental state examination (MMSE)⁸—and mortality for all participants in the ONTARGET and TRANSCEND trials. Individuals were divided into four groups according to MMSE score: 30 points (a perfect score indicating no cognitive impairment), which served as the reference group; 29–27 points; 26–24 points; and <24 points, which is generally associated with clinical cognitive impairment. The trials included 30,959 individuals at high risk of cardiovascular disease (aged ≥55 years with a history of either established cardiovascular disease or diabetes mellitus with evidence of end-organ damage). Both the ONTARGET and the TRANSCEND studies were clinical trials designed to test the effects of hypertension treatment with the drug telmisartan (either alone or in combination with other antihypertension medications) on cardiovascular and cerebrovascular outcomes. O'Donnell *et al.* performed a novel meta-analysis that focused on the association between baseline MMSE performance and the clinical outcomes of coronary artery disease, stroke, congestive heart failure, or cardiovascular death, and a composite outcome of stroke, myocardial infarction, or cardiovascular death (median duration of follow-up 56 months).

As might be expected in individuals at high risk of vascular disease, a history of stroke or myocardial infarction was significantly associated with an increased risk of the composite outcome. Interestingly, the investigators also found a highly significant and graded increase in the risk of stroke, cardiovascular death, hospitalization from congestive heart failure, and the composite outcome as MMSE score declined.¹ An MMSE score of <24 points was associated with a twofold increase in the hazard ratios for all outcomes except myocardial infarction. Moreover, a small change of just two points in MMSE score over time in a subgroup of 4,559 individuals was associated with an increased risk of cardiovascular death, noncardiovascular death, incident stroke, and the composite outcome. No trend was observed between MMSE score and new cardiac events such as incident myocardial infarction or unstable angina. The reason for this lack of relationship is difficult to discern from the data, but one might speculate that baseline MMSE score is an index of cardiac function irrespective of clinical events such as myocardial infarction or angina. The fact that baseline MMSE score was significantly associated with incident congestive heart failure supports this hypothesis.

The investigators propose that “a reduced MMSE score is mostly a marker for covert cerebrovascular disease”.¹ They provide a number of examples to support this proposal, but fail to comment on important baseline differences between the groups that might support their argument. Trends in the baseline prevalence of vascular risk factors and stroke were associated with differences in baseline MMSE score. For example, the prevalence of a history of stroke was 21% and 32% in the groups with the highest or lowest MMSE scores, respectively.¹ Disparities were also recorded in systolic blood pressure, blood glucose levels, and cigarette smoking. Moreover, common protective factors for cardiovascular and cerebrovascular disease, such as moderate alcohol intake and exercise, were lower in groups with a low MMSE score than in those with a high score. For example, 37% of individuals with an MMSE score of 30 points consumed moderate amounts of alcohol and only 23% classified themselves as sedentary, whereas only 19% of individuals with an MMSE score

<24 points consumed moderate amounts of alcohol and 43% classified themselves as sedentary.¹

As described above, a history of vascular risk factors is associated with a more-rapid rate of cognitive decline, even among individuals within the age-range studied by O'Donnell *et al.*^{1,6} Moreover, individuals with evidence of vascular brain injury as determined by a large burden of white matter hyperintensities have an associated elevation in systolic blood pressure, and increase in the incidence of coronary artery disease and stroke, but not hypertension (which reflects the well-established fact that hypertension is commonly underdiagnosed).⁹ Each of these risk factors and vascular outcomes has been associated with cognitive decline and the incidence of dementia,¹⁰ which suggests that these processes are likely to have been present and detrimentally affecting the brain for many years, in the same way that they are known to affect the heart, kidneys, and peripheral circulation.

The conclusion of this study is clear: “impaired cognitive testing with the MMSE is associated with a graded increase in the risk of stroke, cardiovascular death, and hospitalization for heart failure in [the] population of patients at increased cardiovascular risk. A simple cognitive screen provides important prognostic information in patients with a high cardiovascular risk.”¹ Evidence of even subtle brain injury, as determined by MMSE score or another measure, should have a substantial impact on how physicians regard the treatment of vascular risk factors for three important reasons. First, evidence strongly suggests that the impact of vascular risk factors on brain structure and function is continuous. Second, considerable brain injury might precede clinical manifestations by years or even decades, which indicates that prevention of stroke or cognitive impairment requires aggressive treatment early in the natural history of the disease. Third, and possibly most importantly, brain structure and function require the same monitoring as the heart, kidneys, and peripheral vascular system. Current treatment recommendations have had a clear beneficial effect on the average blood pressure in the US population and hypertension-related vascular mortality has declined dramatically. Similar prevention of cognitive decline through management of vascular risk factors has not been achieved. The brain should now be considered an end-organ of vascular disease and treated appropriately.

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Figure 1.

Age-specific prevalence of various vascular diseases (left-hand axis), and brain size as a percentage of intracranial volume ('brain volume'; right-hand axis) from the original and offspring cohorts of the Framingham Heart Study.⁵ Hypertension affects a substantial proportion of the population early and increases steadily with age. The trajectory of the prevalence of hypertension is mirrored approximately 1 decade later by the prevalence of end-organ injury such as coronary artery disease, which is then followed after another decade by an increasing prevalence of stroke. Clinically silent brain injuries, such as brain atrophy or infarction detected by MRI, are closely age-linked with, and might be a consequence of, hypertension.