ALZHEIMER DISEASE AND STROKE

Cognitive and neuroimaging predictors of AD and stroke

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A recent study has examined potential predictive markers of Alzheimer disease (AD) and stroke. The results challenge some current assumptions, suggesting that stroke might often follow a decade of deterioration in brain structure and function, and that cognitive and MRI markers of AD differ in older and younger individuals.


The WHO estimates that stroke was the cause of death in 17.3 million people in 2008, and that annual mortality from this disease will reach 23.3 million by 2030. 35.6 million people have dementia, which has been attributed to Alzheimer disease (AD) in over 50% of cases.1 Moreover, stroke and dementia are first and second, respectively, in the list of neurological disorders that make the greatest contribution to the global burden of disease.2 Accumulating evidence indicates that these major public health challenges share key vascular risk factors, such as hypertension, ischaemic heart disease, hypercholesterolaemia, atrial fibrillation, smoking and obesity.1

A recent study by Weinstein et al.3 evaluated predictors of both AD and stroke in two cohorts from the Framingham Heart Study—the world’s best-known epidemiological study, which encompasses a sample of more than 5,000 adults and now includes a third generation of participants. Although the primary focus of the Framingham Heart Study was cardiovascular disease, it has made important contributions in other areas, including cognitive outcomes and dementia. This and other epidemiological studies, such as the Rotterdam Study, have identified various predictors of stroke and dementia. The findings of Weinstein et al.3 add to the notion that both clinical AD and stroke are the culmination of many years of subclinical decline in brain structure and function.

A strength of the study design was the inclusion of two generational samples. An initial group of 1,456 people completed cognitive evaluations between 1976 and 1978, with a subgroup of 224 undergoing MRI 23 years later. In addition, a sample from the offspring of the original 1976–1978 cohort over the age of 55 years had cognitive assessments (1,679 individuals) and MRI (1,469 individuals) between 1999 and 2004. Incident stroke and dementia were identified in both cohorts through prospective surveillance over 10 years (Figure 1).

The researchers identified white matter lesion volume as a predictor of stroke,3 in agreement with previous studies.4 A new finding by Weinstein et al.3 was that smaller global brain volume was also associated with increased risk of stroke. Corroborating a prior study limited to older men,5 stroke risk was found to be predicted by scores on part B of the Trail Making Test (TMT-B)—a measure that reflects cognitive flexibility, a component of executive function. Interestingly, TMT-B performance, white matter lesion volume and total brain volume had additive effects on risk of stroke, which suggests that each factor modulates stroke risk via a distinct substrate. Investigation of large-vessel or small-vessel pathology, measurement of intima-media thickness, and retinal vascular imaging could be important avenues to identify the mechanisms that mediate these associations.

After adjustment for silent brain infarction, white matter lesion volume was still a significant predictor of stroke, and the association between cognition and future stroke was not attenuated, suggesting that silent infarction is not the sole cause. The results add credence to the notion that a prodromal period of deteriorating brain structure, which begins years before clinical detection and is well known in AD,6 also applies to cerebrovascular disease.

In the offspring cohort, the best cognitive predictors of AD were scores on visual and verbal memory batteries.3 Individuals who scored more than 1 SD below the mean on these tests had a 2.3-fold greater risk of AD compared with individuals with mean scores. Scores on the TMT-B also contributed to the predictive model, emphasizing the importance of executive dysfunction as an early indicator of progressive cognitive decline. In the original 1976–1978 cohort, the best cognitive predictor of AD was score on the Controlled Oral Word Association Fluency Test, which also indexes executive function, suggesting that impairment of executive performance was a central rather
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than an additional predictor of incident AD in these individuals. Weinstein et al.3 identified key differences in structural brain changes associated with AD in the offspring versus the original cohort. In the subgroup of the offspring cohort with MRI data, the key predictor of AD was hippocampal volume, whereas hippocampal volume and total brain volume were both associated with incident dementia in the original cohort. The results suggest that the typical perception of AD as a disease that presents with atrophy of medial temporal lobe structures and amnestic deficits is broadly correct in the offspring cohort, in which the average age was 66 years. In the original cohort, who were in their 80s by the end of the assessment period, total brain atrophy and executive dysfunction were better predictors of incident AD. This difference between cohorts (Figure 1) probably reflects the much greater heterogeneity and pattern of pathology associated with incident AD in older individuals.

The cognitive measure of TMT-B score was a common predictor of both AD and stroke.1 Subtle executive impairment, though less prominent than the core memory deficit, is usually present in early or prodromal AD.7 Executive dysfunction is also characteristic of cerebral small-vessel disease.8 A possible explanation for the commonality of executive dysfunction as a risk factor for AD and stroke is that the neural networks involved are broadly distributed in the brain and are, therefore, vulnerable to a range of insults at various locations.

A number of methodological issues in the recent study1 are worthy of consideration. Relatively few people developed incident AD, particularly in the MRI substudies (28 of 1,469 individuals), limiting the power of subsequent analyses. The low incidence of possible AD is also surprising, especially in the older cohort, in which concurrent pathologies are common. In addition, although surveillance for events was continuous, the MRI and cognitive measures were cross-sectional snapshots, which could be important given that the pattern of association might vary according to the timing, as well as the nature, of an examination. If individual variations in brain structure predominantly reflect vascular factors in the seventh decade but are gradually dominated by AD pathology with increasing age, this would explain why brain volume predicted stroke in the offspring cohort (scanned at a mean age of 66 years), but AD in the original cohort (scanned in their 80s).

What do results such as these mean in practice? In stroke, current concepts of end-organ damage from vascular risk need to be revised. If stroke is a culmination of a decade of deterioration in brain structure and function, heavy weighting of efforts towards secondary prevention might not be the optimal approach. Biomarkers of subtle brain injury should become standard in trials of stroke risk modification, and improved understanding of the prodromal state and associated biomarker profiles should be pursued. For AD, the results point to the importance of executive dysfunction as an early predictor, and differences between cognitive and MRI markers in older versus younger individuals, which have important implications for diagnosis and clinical trial design.