Prestroke Cognitive Function and Cerebrovascular Disease: If They Interact, It May Not Be Through Symptomatic Stroke

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Editorial

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If They Interact, It May Not Be Through Symptomatic Stroke

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In this issue of *Stroke*, Reitz and coworkers explore the link between incident stroke and dementia in data from the Rotterdam Study.[1] The emphasis on *incident* stroke is important: previous studies to address this question have recruited patients at the time of stroke so that prestroke cognitive status has been inferred rather than measured directly.[2,3] Therefore, this is the first truly prospective data to assess the relationship between prestroke cognitive decline, stroke and subsequent dementia. Incident stroke led to a doubling of dementia risk over a mean follow-up time of 3.9 years. An approximate doubling of risk has also been found in other cohorts like those from Rochester and Framingham, so this study provides important confirmation of this size of effect.[2]

Much interest has surrounded the possible mechanisms of this doubling of risk: does stroke have an independent effect or does it accelerate some pre-existing process in the brain? More specifically, does stroke accelerate a pre-existing neurodegenerative process like coincident Alzheimer disease (AD)—a synergy that would fit with the strong epidemiological evidence of the link between vascular risk factors and AD.[4] In the absence of good biomarkers to diagnose neurodegenerative disease at the time of stroke, one way to assess this question indirectly is to infer some pre-existing process from prestroke cognitive decline.

The most important and interesting finding of the study is that no interaction was seen between prestroke cognitive function and stroke on the risk of subsequent dementia. Readers should not be confused about what this means. This does not mean that prestroke cognitive impairment is unimportant and does not contradict studies showing that those with prestroke cognitive impairment have a higher risk of developing dementia.[3] Given that the concept of dementia is based on an arbitrary cognitive threshold it is not surprising that cognitive status, defining the distance a subject has to fall to meet the criteria, predicts dementia at some fixed point in the future. Nor is it that surprising that having a stroke increases this probability. The interesting question—because it may reveal something about the mechanisms that unfold to produce dementia after stroke—are whether these factors interact. The results presented by Reitz et al suggest that they do not, at least within the context of this study. Incident stroke led to a doubling of risk regardless of prestroke cognitive status. Furthermore, the impact of stroke was the same in those at genetic risk for AD (through possession of the ApoE ε4 allele) as in those without this factor, and did not seem to vary according to risk factor profile. Of course those with cognitive decline or with certain risk factors will have a higher baseline dementia risk, but the impact of stroke seems to be a uniform doubling of risk across groups.

The strengths of the study are accurately described by the authors. It is large, prospective and the completeness of follow-up and case ascertainment are good. One advantage of the truly prospective nature is that the authors were able to assess the slope of prestroke cognitive change as well as the level immediately before stroke. This is important as both level and rate of change will determine whether a subject will meet a threshold for dementia at some point in the future. However, one limitation is that assessment of cognition was restricted to the MMSE. The nonlinear nature of this scale, lack of sensitivity to change in some cognitive domains, and vulnerability to practice effects means that the estimation of slope of cognitive change is likely to have been coarse. If anything, however, the use of the MMSE, which is heavily focused toward the cognitive deficits of AD, may have biased the study toward testing an interaction between stroke and prestroke AD, which many would see as the more interesting question. It was not possible to assess this question directly by calculating separate hazard ratios for AD and vascular dementia. Because this distinction would have been based on criteria rather than pathology, incident stroke would have biased the diagnosis of subtype toward vascular dementia, leading to an inevitable circularity. Therefore, the interaction between stroke and prestroke processes in specific dementia subtypes remains an open question.

One limit to the scope of these results that should not be forgotten is that this was a study of *symptomatic* stroke. The Rotterdam Study has also shown us that silent strokes are common, indeed more common than symptomatic events,[5] and cognitively important.[6] Symptomatic strokes will be found for the most part in the sensorimotor systems, where interaction with an ongoing neurodegenerative process may be least likely. Put differently, symptomatic stroke and processes of prestroke cognitive decline may be kept apart by their different spatial locations.

There is also more to cerebrovascular disease than stroke. Aside from lacunar infarction, the cardinal manifestations of small-vessel disease include diffuse white matter lesions, which when confluent are described as leukoaraiosis. Many of the risk factors shared by cerebrovascular disease and AD

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are also shared by acute stroke and these more insidious and progressive manifestations of cerebrovascular disease. Chronic hypoperfusion, not sufficient to induce complete infarction, has long been put forward as a mechanism for diffuse white matter lesions, and recent pathological evidence from the UK MRC Cognitive Function and Ageing Study supports this by showing that inducible factors produced in response to ischemia, such as hypoxia-inducible factors 1α and 2α (HIF1α and HIF2α), are elevated in deep white matter lesions in older adults.[7] Interestingly, evidence is emerging in rats and in vitro models that chronic hypoperfusion may drive the pathological cascade of AD[8] via these factors. Chronic hypoperfusion promotes the accumulation of Aβ, and this effect may be mediated by HIF1α, which promotes expression of the β-secretase enzyme, funnelling more amyloid precursor protein down the amyloidogenic pathway.[9] So there is a molecular rationale to suggest that interaction between cerebrovascular disease and AD can be mediated by diffuse white matter lesions. Furthermore, this is only one of a number of potential mechanisms that could account for the relationship between white matter lesions and circulating Aβ found in a range of subjects including those with AD, mild cognitive impairment and community-dwelling carriers of the ApoE ε4 allele.[10,11]

Understanding the broader impact of cerebrovascular disease and stroke on cognitive function and the burden of dementia is a major research goal. This study suggests that the impact of symptomatic stroke on dementia risk is independent of prestroke cognitive status and other baseline characteristics. Further studies with detailed imaging will help to determine whether silent infarcts, or infarcts in specific locations, interact with pre-existing processes in the brain. Furthermore, in looking for interactions with AD, nonstroke manifestations of cerebrovascular disease, like diffuse white matter lesions, are also promising candidates. In the meantime, physicians should continue to see poststroke dementia as an important target for secondary prevention and bear in mind the results of trials like PROGRESS[12] and Syst-Eur,[13] though new strategies and more data are needed.

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Disclosures

None.

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