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When two are worse than one:

Stroke and Alzheimer disease

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In this issue of *Neurology*, Regan et al.¹ present longitudinal follow-up of 224 patients with clinically diagnosed Alzheimer disease (AD) and cerebrovascular risk factors in order to assess the potential role of cerebrovascular disease (CVD) on the course of cognitive decline associated with AD. The aim of this study was based on the recognition that CVD is a coincident finding in more than one third of patients with AD at postmortem examination and is associated with a significantly greater likelihood of expressed dementia for a given level of AD pathology.^{2,3} Cerebrovascular risk factors are also associated with late life brain changes and subtle cognitive impairment even among older individuals considered cognitively normal.^{4–6} Moreover, stroke is associated with a significantly increased risk for future dementia.^{7,8} Understanding the impact of CVD on dementia is also relevant to dementia treatment. No treatment improves AD, but treatment of CVD is associated with reduced incidence of dementia among high-risk populations,⁹ including individuals with previous stroke,¹⁰ offering hope that incident dementia (even incident AD) could be reduced through risk factor management.

Incident stroke occurred in approximately 3% of subjects studied by Regan et al.¹ over 18 months and they found that incident stroke was the only risk factor significantly associated with increased rate of cognitive impairment in this cohort of subjects initially diagnosed with AD. This finding is not surprising given that a second brain injury during the course of AD is likely to accelerate cognitive decline, although at advanced stages of AD, the cognitive impact of stroke may go undetected. Surprising, however, was the frequency of stroke in this small convenience sample and the absence of effects from concomitant vascular risk factors such as hypertension, diabetes, or homocysteine.

There are a number of explanations for the lack of association between CVD risk factors and cognition in AD. Most obvious was the relatively low prevalence of CVD risk factors among the subjects studied. For example, the prevalence of CVD risk factors was substantially lower than a similarly aged sample of stroke and dementia subjects from the Framingham Heart Study where 81% had hypertension.⁸ The prevalence of CVD risk factors, however, does not seem well correlated with incident stroke among older subjects. For example, a second study by Gamaldo et al.¹¹ of subjects participating in the Baltimore Longitudinal Study of Aging, also in this issue of *Neurology*, reports that incident stroke significantly increased risk of dementia, but similar to Regan et al.¹ did not find an effect of CVD risk factors on dementia risk. The prevalence of CVD risk in the Gamaldo et al. study¹¹ was very similar to that reported by Regan et al.¹ Despite a lower prevalence of

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known CVD risk factors for both studies, incident stroke was substantial, confirming the high incidence of CVD among these individuals. These data suggest that concurrent measures of recognized CVD risk factors may not accurately reflect the extent of prevalent CVD among older individuals. This is consistent with the observation that pathologic evidence of vascular injury, particularly microvascular injury, may be as frequent as Alzheimer pathology in select postmortem samples.¹² It also suggests the need for other methods to detect asymptomatic CVD among older individuals.

Alternatively, vascular risk factors may have only a small impact on cognition as compared to the AD process. There is considerable support for this second hypothesis as well. Previous reports³ indicate that the greatest effect of CVD on risk for dementia occurs when AD pathology is mild. The data by Gamaldo et al.¹¹ support this observation. They note that the impact of stroke in their sample was only significant for individuals already suffering from mild cognitive impairment whereas individuals with normal cognition at the time of stroke did not have an increased risk for future dementia. Cerebrovascular risk factors, therefore, may have the greatest influence on the trajectory of brain aging, thereby acting to increase the susceptibility to late life cognitive impairment from other processes such as AD.¹³

Regan et al.¹ clearly document that stroke is common and debilitating to patients with AD. Since stroke is preventable through treatment of recognized risk factors and since such treatments may reduce susceptibility to late life dementia, it is incumbent upon us to treat what we can.

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