Brain Microbleeds and Cognitive Function

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See related article, pages 1949–1951.

There has been increasing recognition of the role of cerebrovascular disease and its risk factors in the etiopathogenesis of dementia in older persons.1,2 Cerebral infarcts, white matter changes, hypertension, and diabetes have all been implicated as causal agents or risk factors for dementia.3 The public health impact of cerebrovascular disease on dementia is underscored by the observation that up to one third of older individuals have cerebral infarcts by neuroimaging4 or pathology,5 many without clinically recognized stroke.4–6 These infarcts, often subcortical in location,4–6 not only can result in dementia,7 but may also add to cognitive impairment,8 lower the threshold for dementia,8 and have a synergistic effect with Alzheimer disease pathology.9 Subcortical infarcts are most often secondary to small vessel disease, pathologically identified by lipohyalinosis of the straight penetrating arterioles. Hypertension and diabetes are both risk factors for this pathology and thereby risk factors for subcortical infarcts. Vessel wall changes can lead to hemorrhage as well as infarction. When the leakiness of blood vessels results in small amounts of extravasated blood and ultimately hemosiderin, this is known as microbleeds. Microbleeds are defined as small hemorrhages recognized by their small round homogenous low signal appearance on gradient-echo T2* MRI. In addition to their diagnostic and prognostic markers,12 microbleeds have also been pathologically linked with amyloid angiopathy.10,11 Clinically, microbleeds have been associated with cerebrovascular disease and some of its risk factors, including lacunar infarcts, hemorrhages, white matter changes, and hypertension.12 Microbleeds have also been reported to be increased inBinswanger disease,13 mild cognitive impairment and Alzheimer disease.14 Over the past decade, interest in microbleeds has increased as possible diagnostic, therapeutic and prognostic markers.12 However, the possible cognitive effects of microbleeds have remained relatively unexplored. In subjects from a memory clinic, microbleeds were increased in mild cognitive impairment and Alzheimer disease, but there was no relationship between microbleeds and Mini-Mental State examination (MMSE).14 Another study found that in persons with cerebrovascular disease, microbleeds had a striking effect on executive function, but no effect on “current intellectual function” or other cognitive domains, including memory, language and visual-spatial skills.15

In this issue of Stroke, Seo et al report the relationship between microbleeds as seen on gradient-echo T2* MRI and cognitive function in subcortical vascular dementia.16 Eighty-six subjects with subcortical vascular dementia from a memory disorder clinic were retrospectively evaluated for number of microbleeds (≤10 mm in size, 1.5-T MRI scanner [GE Signa], 20 axial slices) and scores on neuropsychological tests, including tests of attention, verbal memory, visual memory, language, visuospatial function and frontal executive function, and MMSE and Clinical Dementia Rating Scale (CDR). The authors excluded potential mimics, including lesions associated with the subarachnoid space, calcifications, vascular malformations and traumatic brain injuries. Neuroimages were blindly evaluated for ischemic changes. The authors found microbleeds in almost 85% of their patients with subcortical vascular dementia. In analyses controlling for age, education, lacunar infarcts, and severity of ischemia, Seo et al found that microbleeds were related to all the cognitive domains with the exception of language function which was marginally significant (P=0.06). Microbleeds were also related to MMSE, while the relationship with CDR was marginally significant (and P=0.052). The authors concluded that microbleeds may be an important mechanism for cognitive impairment in persons with subcortical vascular dementia.

It is perhaps not surprising that microbleeds may be associated with their own neurocognitive effects, because pathologically microbleeds may be associated with tissue necrosis.10 In this way, depending on their location, size and number, microbleeds may be hypothesized to cause specific or more widespread damage and affect single or multiple cognitive domains. It is interesting to note that in the study of Seo et al, most of the microbleeds were found in the temporoparietal regions of cortex.16 These results are similar to another study of vascular dementia (Binswanger disease)13 but contrasts with a study in patients with cerebrovascular disease which found microbleeds in the basal ganglia and frontal region and associated executive dysfunction.15 Given that the cohort was derived from a memory clinic and the microbleeds were predominantly cortical, it is likely that these microbleeds are marking not only lipohyalinosis but also amyloid angiopathy in these dementia patients. Indeed, many persons with vascular dementia are found to have mixed dementia (Alzheimer disease and cerebral infarcts) at autopsy.17 Because amyloid angiopathy may reflect underlying Alzheimer disease pathology, it will be important in future studies to investigate whether microbleeds are an independent contributor to cognitive impairment in vascular dementia or reflect associated Alzheimer disease pathology.

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An association of microbleeds with cognitive impairment may provide a mechanism by which vascular risk factors, such as hypertension, could impair cognition separate from infarcts and white matter changes. In addition, microbleeds could account, in part, for the variability of cognitive impairment from both subcortical infarcts and Alzheimer disease pathology. Microbleeds are common in persons with cerebrovascular disease and with Alzheimer disease, and these are the most common age-related pathologies in the brain. Indeed, because microbleeds are small, require gradient-echo T2* sequences, or a careful pathological survey, their importance in cognitive impairment in older persons could be significantly underrecognized.

The main strengths of this study are analyses that controlled for potential confounders including age, infarcts, and white matter changes, and the large number of scan images. Limitations include possible selection bias through a memory disorder clinic and the retrospective study design. Future studies that prospectively investigate the effect of microbleeds on the cognitive impairment of vascular, Alzheimer, and mixed dementias in diverse cohorts will be important.

Disclosures
None.

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