Cerebral microinfarcts

Enumerating the innumerable

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Neurology® 2013;80:1358–1359

Microinfarcts are small areas of tissue rarefaction or cavitation presumed to be caused by ischemia.[1] Because of their small size, they cannot be seen by the naked eye on postmortem examination of the brain, but only by microscopy. They are seen at autopsy in 16% to 46% of elderly dying of all causes, but are more common in patients that die with a history of dementia.[1,2] Data from community-based autopsy studies suggest that microinfarcts are independently associated with the risk of dementia, and indeed may be more strongly associated with dementia than other more readily visible cerebrovascular lesions such as lacunar infarcts and white matter lesions of presumed vascular origin.[2]

To examine a brain for microinfarcts, the neuropathologist first cuts roughly 8 to 18 blocks of paraffin-fixed tissue, approximately 1.5 × 3 × 0.25 cm in volume, from selected brain regions. The most superficial 4 to 6 μm of tissue is sectioned from the block by a microtome, stained with hematoxylin & eosin and affixed to a slide, and then viewed under the microscope. Typically, no more than a handful of microinfarcts are identified, and often only a single microinfarct is seen in the slides. However, the neuropathologist visualizes only about 0.2 cm^3 of tissue, out of an average brain volume of approximately 1,350 cm^3 (0.015% of the overall volume). What lurks, undiscovered, in the terra incognita comprising the more than 99.9% of brain volume that is not visualized?

In this issue of *Neurology*®, Westover et al.[3] use a combination of mathematical modeling and intensive sampling to enumerate the previously innumerable number of microinfarcts in the whole brain. To do this, they modified a mathematical technique used to solve the "Buffon needle problem" to estimate the most likely number of microinfarcts across the whole brain, with 90% confidence limits, given visualization of a specific number of microinfarcts on 9 slides. Their astonishing finding is that seeing a single microinfarct among 9 slides suggests the presence of 552 microinfarcts across the entire brain. Even when no microinfarcts are seen, one cannot exclude with more than 95% confidence that up to 1,653 remain undiscovered in the unexamined tissue. The 90% confidence limits around the estimated numbers of microinfarcts were large and overlapped for different numbers of visualized microinfarcts, as shown in figure 2 of the article. To validate their findings, the authors examined up to 80 additional sections in 2 patients and found additional numbers of microinfarcts that were consistent with their mathematical estimates. Further validation will be needed to determine the accuracy of several assumptions underlying the model: that microinfarct distribution is uniform across the brain, that microinfarct volume can be approximated as a sphere, and that microinfarcts are not confluent (i.e., they do not overlap).

These findings make it clear that studies to date have estimated the burden of cerebral microinfarcts very crudely, detecting only the tip of the iceberg. Indeed, it is remarkable that strong associations between microinfarcts and cognition have been detected[2] given the measurement error inherent in sampling such a limited fraction of the brain tissue. Our understanding of the risk factors and consequences of microinfarcts would certainly be enhanced if patients could be accurately ranked according to their true number of microinfarcts. However, more intensive neuropathologic examination does not seem to be a practical solution. Even with more intensive sampling, with up to 10 times more slides reviewed than for a routine autopsy case, the width of the confidence interval remains quite large—more than 500—for a hypothetical example patient with 1,000 microinfarcts (as shown in supplemental figure 5).

Neuroimaging may be the key to comprehensively evaluating the total burden of cerebral microinfarction, because with MRI, the entire brain can be visualized. Although microinfarcts are invisible on conventional MRI because of their small size (with typical diameter of 0.2–0.5 mm), larger microinfarcts can be visualized on high-field-strength, ex vivo MRI of brain tissue at 7 tesla (T).[4] Importantly, detection of these larger microinfarcts is now, for the first time, also possible in vivo. A recent 7T study detected 15 lesions likely to represent cortical microinfarcts (diameters ranging from 0.5 to 3 mm) in 6 of 22 functionally independent elderly subjects without a known history of dementia.[5] In retrospect,

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

several of these lesions proved to be visible at 3T MRI as well, albeit less distinctly. This raises the possibility that microinfarcts may contribute to heterogeneity in cortical signal intensity or cortical thickness on 3T MRI, which then could be detected by quantitative methods, even if the microinfarcts themselves do not appear as distinct lesions that can be identified with sufficient confidence. Additionally, recent studies show a surprisingly high incidence of asymptomatic small areas of restricted diffusion in patients with cerebral small-vessel disease manifesting as symptomatic intracerebral hemorrhage, suggesting the possibility that these small areas of restricted diffusion may be acute microinfarcts caught in evolution.[6,7]

With their objective estimates, Westover et al. have for the first time identified the potential scope of the problem of microinfarcts. Given the hundreds or thousands of microinfarcts that may accumulate in the brain, it is plausible that these lesions could cause cognitive impairment and confer increased risk for dementia, as suggested by epidemiologic studies, and therefore could be a target for vascular risk reduction strategies. A practical means of converting the innumerable to the numerable, potentially based on neuroimaging of microinfarct number or a validated close surrogate, will be a necessary step to enable studies to test whether preventing microinfarcts reduces the risk of brain dysfunction and dementia.

AUTHOR CONTRIBUTIONS

Eric Edward Smith: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Geert Jan Biessels: drafting/revising the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

E. Smith has received research funding from the NIH (R01 NS062028), Canadian Institutes of Health Research, Alberta Innovates–Health Solutions, Canadian Stroke Network, Heart and Stroke Foundation of Canada, C5R, and the Alzheimer Society of Canada. G.J. Biessels has received research funding from The Netherlands Organisation for Health Research and Development (VIDI grant number 91711384), the Netherlands Heart Foundation (grant number 2010T073), the International Foundation for Alzheimer Research, and The European Foundation for the Study of Diabetes; and serves as a consultant for Boehringer Ingelheim AB and Takeda Pharmaceuticals. Go to Neurology.org for full disclosures.

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