Focal cortical thinning is caused by remote subcortical infarcts

Spooky action at a distance

In this issue of *Neurology*®, Duering et al.¹ present compelling proof-of-principle evidence that small subcortical infarcts have remote consequences on gray matter volume. Using MRI scans acquired before and after an incident subcortical infarct, they were able to show that the appearance of a new subcortical infarct was associated with cortical thinning in connected brain regions.

Unique features of the study design allow the reader to conclude that small subcortical infarcts probably cause cortical thinning directly, and are not merely correlated phenomena. A review of serial MRI scans from a longitudinal cohort study of patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) allowed the identification of pairs of MRI in which a new small subcortical infarct was apparent on the follow-up scan, indicating that an incident infarct had occurred between the 2 examinations. The authors hypothesized that the new infarct would cause focal cortical thinning in connected brain regions. Diffusion tensor imaging with tractography was used to identify the brain regions that may exhibit cortical thinning. Importantly, tractography was done on the preinfarct scan, which avoids confounding of the tract identification process by the infarct itself. Then, cortical thinning in the identified cortical regions of interest was measured, and a highly significant 9% selective decrease in cortical thickness in connected regions was documented.

These findings illustrate a mechanism by which subcortical ischemic damage might contribute to cortical thinning, brain atrophy, and cognitive decline. Brain atrophy can be the end stage of multiple pathologic processes and is a well-recognized feature of many neurologic diseases, including Alzheimer disease and multiple sclerosis. Atrophy is a feature of cerebral small vessel diseases.² Progressive gray matter atrophy occurs in lacunar stroke patients with poststroke mild cognitive impairment.³ More than 50% of lacunar stroke patients develop neuropsychological disturbances (mainly executive disorders) after a first lacunar infarct,⁴ and both gray and white matter changes seem to contribute to cognitive impairment. In the Austrian Stroke Prevention study of healthy older persons, an increase in MRI white matter hyperintensities of presumed vascular origin was associated with a decrease in brain volume and cognitive decline.⁵ In patients with CADASIL, atrophy is the single brain imaging characteristic that is most closely associated with cognitive function and clinical disability, possibly reflecting that atrophy is the final common pathway of damage caused by diverse manifestations of cerebral small vessel diseases such as lacunar infarcts, microinfarcts, and white matter lesions.⁶

In the study of Duering et al.,¹ the mechanism of action for cortical thinning “at a distance” could not be determined because it would probably require neuropathologic examination. Although Einstein famously derided distant quantum effects as “spooky action at a distance,” in this case the distant effects may not be so spooky—the authors reasonably speculate that disruption of axons by the infarct led to retrograde or anterograde (transsynaptic) degeneration of connected neurons. Nonspecific global effects were excluded by expressing regional cortical thinning as a fraction of global whole-brain cortical thinning and by a comparison with control seed regions placed in the homologous region in the contralateral hemisphere in noninfarcted tissue.

These data strongly support the inclusion of focal cortical atrophy as another of the many neuroimaging manifestations of CADASIL, and probably other cerebral small vessel diseases too. Because CADASIL manifests in relatively younger persons without confounding neurodegenerative diseases and with a relatively low burden of traditional vascular risk factors, CADASIL may be considered a prototype disease for studying the consequences of pure subcortical ischemia and infarction. It is reasonable to infer that sporadic small subcortical infarcts, which are vastly more common than CADASIL, also cause cortical thinning, but this must be tested directly in longitudinal studies. Also, studies that combine white matter tractography by diffusion tensor imaging with autopsy data would be helpful to elucidate further the relationship between subcortical damage and gray matter atrophy. The advanced imaging methods employed by Duering et al.¹ failed in many patients

1. Duering et al. (2012). *Neurology*®
2. Go to Neurology.org for full disclosures. Disclosures deemed relevant by the authors, if any, are provided at the end of this editorial.
for technical reasons, possibly related to the many imaging abnormalities associated with CADASIL. Additional work may be needed to develop robust neuroimaging computational analytic pipelines for the highly abnormal brains affected by severe cerebral small vessel diseases.

The study by Duering et al.\textsuperscript{1} shows us that small subcortical infarcts can cause focal cortical thinning, but additional studies will be needed to determine what proportion of global brain atrophy is explained by this phenomenon. The exact pathologic underpinnings of atrophy are unclear and probably vary by disease, but could include synaptic loss, apoptosis or necrosis of neurons or other cells, shrinkage of cells, decreased blood volume, or other mechanisms. In the case of subcortical small vessel disease, it is not clear whether small infarcts are associated with atrophy solely due to direct effects including neuronal degeneration, or whether they could also be markers for other shared factors, such as hypertension, that independently cause both cerebral small vessel disease and brain atrophy by different mechanisms. Moreover, whether other cerebrovascular lesion types, such as microbleeds or focal white matter lesions without infarction, can cause focal cortical thinning is unknown. Finally, the consequences of focal cortical thinning on brain metabolism, network function, and cognitive and other outputs are also unclear but worthy of study. Indeed, the remote "action at a distance" may be the key to solving the riddle of why small subcortical infarcts have such large consequences on cognition.

DISCLOSURE
E.E. Smith has received grant funding from the National Institute of Neurological Disorders and Stroke (R01 NS062028), Canadian Institutes of Health Research, Alberta Innovates–Health Solutions, Canadian Stroke Network, Heart and Stroke Foundation of Canada, CSR, and the Alzheimer Society of Canada. A. Arboix has received grant funding from the Fondo de Investigación Sanitaria (FIS PI081514), Instituto de Salud Carlos III, Madrid, Spain. Go to Neurology.org for full disclosures.

REFERENCES