Interaction of Vascular Damage and Alzheimer Dementia: Focal Damage and Disconnection[1]

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Conflicts of interest are listed at the end of this article.

See also the article by Meng et al in this issue.

Dementia is a major health and socioeconomic problem with ever-increasing prevalence due to the increasing age of the population (1). Alzheimer disease (AD) and vascular dementia are both common disorders in the elderly, and although they are commonly co-occurring, they are generally considered to be separate nosologic entities. Neuroimaging biomarkers have evolved considerably over the past decade and demonstrate new insights into disease mechanisms in dementia. Of particular interest is the evolving view of interaction between pathophysiological mechanisms in AD and vascular dementia, as demonstrated with neuroimaging.

Imaging Biomarkers for "Pure" AD

Large-scale databases, such as the Alzheimer Dementia Neuroimaging Initiative (2), provide detailed and sophisticated imaging biomarkers, including structural magnetic resonance (MR) imaging measures such as hippocampal volume, structural connectivity derived from diffusion-tensor imaging (DTI), functional connectivity derived from functional MR imaging, and perfusion from arterial spin labeling, as well as molecular imaging biomarkers such as amyloid and tau positron emission tomography. Many AD studies, notably the Alzheimer Dementia Neuroimaging Initiative, have excluded patients with vascular pathology findings, which is a good choice if one wants to study disease mechanisms in patients with "pure" AD. However, since vascular pathologic processes are common in the elderly and increase with age, there is a concern that such studies in fact do not include "normal" control subjects but rather "super-normal" control subjects and patients with "pure" AD rather than "typical" AD. One might therefore critically question how well these biomarkers perform in a real-world scenario with mixed pathologic processes.

Common Risk Factors for AD and Vascular Dementia

There is increasing awareness that AD and vascular dementia share many risk factors—notably vascular risk factors (3). At the same time, considering the amyloid cascade hypothesis as the unique pathway to AD (4) is increasingly being questioned (5,6). There is growing interest in the role of other contributing factors, such as nutrition, exercise, lifestyle, and—in particular—traditional vascular risk factors, such as obesity, hypertension, or diabetes in dementia, on the basis of evidence from human clinical studies (7,8), postmortem human studies (9,10), and animal models (11). The presence of white matter hyperintensities on MR images, which reflects vascular damage, can be used to predict, for example, future cognitive decline and diagnosis of AD (12) and represents an early and independent predictor of AD risk (13). This suggests that vascular damage is an additional factor that contributes to the development of AD, either by accelerating amyloid deposition or by independently invoking downstream events, such as formation of neurofibrillary tangles and neuronal loss.

Existing Imaging Biomarkers for Vascular Dementia

As the interest in the vascular contribution to dementia grows (1,14), there is also increasing need for imaging biomarkers for pathologic processes induced by vascular disease and risk factors. While, as discussed earlier, imaging biomarkers for neurodegenerative and in particular AD pathologic processes have become progressively

refined and sophisticated over the past decade, imaging biomarkers for vascular damage have evolved less. Acute ischemic lesions can be visualized by using diffusion imaging, and chronic infarcts can be identified with standard MR imaging pulse sequences. The association between visible ischemic lesion burden and cognitive impairment, however, is only modest (15,16).

Many studies have focused on focal white matter hyperintensities on fluid-attenuated inversion-recovery, or FLAIR, MR images, often rated by using simple visual scales like the Fazekas score reported in 1987 (17) or the more refined Scheltens score described in 1993 (18). In clinical practice, both scores provide simple visual rating scores of the global white matter hyperintensity load on T2-weighted or FLAIR images, which correlates with global functional decline in elderly patients (19), dementia, stroke, and death (20). Since the brain has strict spatial organization, it is not surprising that such global white matter hyperintensity scores do not correlate well with specific neuropsychological deficits, as we may expect that specific neuropsychological deficits are related to lesions in specific anatomic locations. Moreover, histopathologic-radiologic correlation demonstrates that T2-weighted or FLAIR MR imaging may lead to overestimation of pathologic demyelination in the periventricular region but underestimation of demyelination in the deep white matter region, presumably owing to the higher local water concentration in the periventricular region and the increasing plasma leakage during aging (21). This is paralleled by higher clinical relevance of white matter hyperintensities in the deep white matter (22,23). Moreover, cortical microinfarcts are another manifestation of small-vessel disease and are increasingly visualized by using high-field and ultra–high-field MR imaging (24).

To overcome the limitations of conventional pulse sequences (and simple visual rating scales), there is a need for quantitative imaging biomarkers of vascular pathology findings beyond visible lesions to assess, in more detail, the effect of concomitant vascular and neurodegenerative pathology findings on cognitive decline. Other studies indicate that DTI may demonstrate much more widespread damage in patients with vascular impairment (25,26).

White Matter Skeleton DTI: A New Imaging Biomarker of Subcortical Disconnection for Vascular Cognitive Disorder

In this issue of *Radiology,* Meng et al (27) studied the effect of vascular damage on cognition in patients with carotid stenosis and propose a novel imaging biomarker for vascular pathology findings on the basis of DTI. The DTI data were processed by using the FSL (FMRIB [Functional MR Imaging of the Brain] Software Library; *http://fsl.fmrib.ox.ac.uk/fsl/*) software package, and the mean diffusivity within the white matter skeleton was identified as the best-performing imaging biomarker to predict probable vascular cognitive disorder (area under the receiver operating characteristic curve, 0.82; 95% confidence interval: 0.75, 0.90). In contrast to manually outlining focal white matter hyperintensity lesions (or more global Fazekas or Scheltens scores), this novel mean diffusivity white matter skeleton biomarker is an operator-independent biomarker that provides a continuous and absolute value, taking into account subcortical disconnection of structural neural networks, and clearly outperformed the classic lesion probability maps, indicating that damage is much more widespread than would appear to the naked eye. Of note, this novel biomarker was successful in the absence and the presence of presumed comorbid Alzheimer pathologic processes, assessed as presence of medial-temporal lobe atrophy (no data available on amyloid status). This indicates that this novel vascular biomarker can be successfully applied even in the presence of comorbid neurodegenerative pathologic processes.

As illustrated in Figure 3 in the study of Meng et al (27), the global cognitive status correlated with diffuse mean diffusivity alterations that occurred across the entire white matter skeleton throughout the brain, while fluency—as an example of a specific cognitive function—was related to more localized mean diffusivity alterations in the forceps minor and the anterior part of the corpus callosum. This indicates that the results of the study by Meng et al could be extended by generating multiple functionally specific regional skeleton masks instead of one whole-brain skeleton—for example, reflecting the established default mode network, working memory network, and executive control network. Such specific subskeletons would likely improve the specificity of the findings with regard to given neuropsychological tasks. Other extensions could be to derive DTI-based graph measures in which the whole brain is treated as a network.

Toward Integrated Imaging Biomarkers of Vascular and Neurodegenerative Pathology Findings

The results of Meng et al (27) suggest again that concomitant vascular and primary neurodegenerative pathologic processes are independent; others have suggested they may even be supra-additive (28)—that is, the combined effect of both vascular and neurodegenerative pathologic processes is more pronounced than the simple linear addition of the two effects. This reinforces the notion that both vascular and neurodegenerative pathologic processes should be carefully assessed in cognitive decline and that there is a need in particular for novel and more precise vascular imaging biomarkers such as the DTI-derived skeleton mean diffusivity suggested by Meng et al (27), not only in vascular dementia but also in "typical AD," which is likely to be affected by both vascular and neurodegerative pathologic processes. In fact, vascular damage may accelerate the AD pathologic process and therefore contribute to cognitive impairment directly and indirectly (1) and deserves more attention in the (secondary) prevention and treatment of patients with cognitive decline, including those with AD and those suspected of having AD.

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