We address 2 issues that may have impact on vascular cognitive impairment (VCI): delirium after acute stroke and the interaction among small vessel disease (SVD), brain atrophy, and degenerative mechanisms. Delirium is an acute confusional state, and it is estimated that as many as 1 in 8 patients experience delirium after acute stroke.\textsuperscript{1-3} Brain atrophy is a predictor of poor outcome in a number of neurological disorders. We discuss the coexistence of degenerative and vascular changes in VCI.

Delirium After Acute Stroke

Risk Factors and Associated Outcomes

Delirium after acute stroke is likely to occur in the first week after hospitalization. In one recent study of 527 consecu-
tive hospitalized stroke patients who had a mean age of 72 years, independent risks for delirium were history of preexist-
tent cognitive decline and infection, right hemisphere stroke, carotid artery circulation large artery stroke, high National Institutes of Health Stroke Scale score, and brain atrophy.\textsuperscript{2} Also, delirium was associated with duration of hospitalization, mortality, and worse functional status.\textsuperscript{2} In a systematic review and meta-analysis of 10 studies encompassing 2004 patients, stroke patients had higher inpatient mortality and mortality at 12 months compared with nondelirious patients, longer hospitalizations, and were more likely to be discharged to nursing homes or for other institutional care.\textsuperscript{4}

Stroke and Postoperative Delirium

Delirium is common after surgery in the elderly, especially after cardiac surgery in which it may affect up to 75\% of patients.\textsuperscript{4} It may take the form of postoperative cognitive decline as an early postoperative delirium (acute cognitive dysfunction) or a later onset and more persistent postopera-
tive cognitive decline.\textsuperscript{5} There is a host of risk factors associated with the development of postoperative delirium. These include but are not limited to factors, such as age, education, comorbidities, history of alcohol or drug use, duration of sur-
gical procedure, apolipoprotein E4 status, and preoperative depression.\textsuperscript{5}

The cognitive trajectory in persons who have undergone major cardiac surgery and who develop delirium is striking. For example, based on a Mini Mental Status Examination score, these persons may have a larger drop in cognition 2 days and at 1 and 12 months after surgery than those without delirium, and after adjustment of baseline differences, between group differences in the Mini Mental Status Examination score are significant at 1 month but not at 6 or 12 months ($P=0.056$).\textsuperscript{4} Furthermore, those with delirium were less likely to return to their baseline level of cognition at 6 months (40\% versus 24\%; $P=0.01$) but the difference was not significant at 1 year (31\% versus 20\%; $P=0.055$).\textsuperscript{4} Therefore, the trajectory of cognitive decline in persons with postoperative delirium may be characterized by initial decline and pro-
longed impairment.

A risk score has been devised that includes preoperative predisposing factors for delirium of which stroke is one of the factors.\textsuperscript{5} Major factors are age $\geq$ 80 years and dementia or recent delirium. Minor features include history of stroke; older age (70–79 years); mild cognitive impairment; functional disability; high medical comorbidity including cardiovascular risk factors, alcohol, and sedative abuse; and depressive symptoms.

The pathogenesis of postoperative cognitive decline is not well defined but may include activation of the immune system to initiate an inflammatory response or anesthetic-induced neurotoxicity.\textsuperscript{5} When there is sepsis-associated encephalopathy, pathophysiology may include involvement of several major neurotransmitter pathways, mitochondrial, endothelial and blood brain barrier dysfunction, brain cell death, abnormal calcium homeostasis, and activation of inflammatory mediators and the complement system.\textsuperscript{6}

Coexistence of Degenerative and Vascular Changes in VCI

Degenerative and vascular mechanisms may coexist at the pathological level in patients with cognitive impairment, particularly in older age.\textsuperscript{7,8} In a study of 54 normal subjects, cognitive performance was studied in relation to vascular features on magnetic resonance imaging and amyloid imaging.\textsuperscript{9} No interaction was found between measures of cerebrovas-
cular disease and Pittsburgh Compound B-positron emission
tomography measures. Lee et al\textsuperscript{10} used positron emission tomography amyloid imaging (Pittsburgh Compound B) in patients in their seventies with clinical and neuroimaging features of subcortical vascular dementia (ie, extensive white matter lesions [WMLs]) and no territorial infarct. They found that \(\approx 70\%\) had no evidence of degenerative change in their brain and that these patients performed better on memory tasks than the Pittsburgh Compound B-positive patients.\textsuperscript{10}

**Brain Atrophy in Association With VCI**

The independent contribution and interaction of medial temporal lobe atrophy (MTA), cortical and subcortical atrophy, and WML volume on cognitive decline were examined in the Leukoaraiosis and Disability Study.\textsuperscript{11} After 3-year follow-up, medial temporal lobe atrophy and subcortical atrophy predicted significantly a steeper rate of decline in global cognitive measures and composite scores for psychomotor speed, executive function, and memory after adjusting for other predictors of cognitive decline. Cortical atrophy independently predicted decline in psychomotor speed with WML volume significantly associated with cognitive decline even after controlling for atrophy scores. A significant synergistic interaction was found between WMLs and atrophy measures in overall cognitive performance across time and the rate of cognitive decline. A synergistic effect was also observed between baseline lacunar infarcts and all measures of atrophy on change in psychomotor speed.

Patients with SVD have various degrees of brain atrophy. It is uncertain whether this reflects the aging process, the concomitant presence of a degenerative mechanism, or is related to subcortical vascular changes.

Nikitunan et al found that patients with SVD, in comparison with age- and sex-matched controls, had a significant smaller brain volume.\textsuperscript{12} Moreover, in SVD patients, there was a significant association between brain volume and executive function. Finally, progression of brain atrophy was higher in SVD patients than in controls. These data suggest that brain atrophy is part of the SVD pathological spectrum and is not a coincidental finding, a conclusion supported by the Cardiovascular Health Study.\textsuperscript{13}

Similar findings were recently reported by the SMART-MR Study (Second Manifestations of Arterial Disease-Magnetic Resonance).\textsuperscript{14} In 565 patients in their sixth decade with symptomatic atherosclerotic disease but without large infarcts, periventricular WML volume at baseline and its progression were independent of vascular factors, associated with greater decrease in cortical gray matter volume and greater increase in ventricular volume. Also, lacunar infarcts at baseline was associated with greater decline in total brain volume, whereas progression of lacunar infarcts with a greater decrease of total brain and cortical gray matter volume. In cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy, a genetically transmitted form of SVD, where neurodegenerative mechanisms are thought to be absent, cortical atrophy was related to lacunar lesions and clinical worsening.\textsuperscript{15}

In summary, the interaction between vascular and degenerative factors is complex and in VCI and SVD, brain atrophy is not likely to be a coincidental finding.

**Disclosures**

Dr Gorelick has nothing to disclose in relation to this manuscript. Dr Pantoni is a deputy coordinator and publication coordinator of the Leukoaraiosis and Disability Study.

**References**

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血管性認知障害の進歩
Advances in Vascular Cognitive Impairment

Philip B. Gorelick, MD, MPH; Leonardo Pantoni, MD, PhD

本論文は血管性認知障害（VCI）をめぐる脳卒中後せん妄、および萎小血管病、脳萎縮、変性病態の相互作用という2つの重要な問題を扱っている。

脳卒中後せん妄

脳卒中後せん妄は脳卒中患者で高頻度に見られ、特に高齢者では高頻度にみられ、特に高齢者では高頻度にみられ、特に高齢者では高頻度にみられ、特に高齢者では高頻度にみられる。脳卒中後せん妄の発症には、年齢、教育歴、既往歴、アルコールや薬物使用歴、手術時間、apo E4遺伝子型、術前の抑うつなどが関与する。心臓手術後のせん妄患者の認知機能を評価すると、1カ月後には有意に低下しており、発症前のレベルに復する確率は6カ月でもまだ有意に少なかった（40% vs 24%；P=0.01）。せん妄の発症を予測するスコアでは、年齢（80歳以上）、認知症、最近のせん妄が主要な因子であった。

血管性認知障害（VCI）における変性病態と血管病理の共存

変性病態と血管性機序は認知機能障害のある高齢者で病理学的に併存する。しかし、皮質下血管性認知症の患者の70%はアミロイドPET陰性であり、陰性群は陽性群より記憶力が良好であった。

血管性認知障害と脳萎縮：Leukoaraiosis and Disability Study（LADIS）では、内側頭葉萎縮と皮質下萎縮が、総合的認知機能および精神運動速度・実行機能・記憶の総合評点の急速な悪化の予測因子であった。皮質下萎縮は精神運動速度の独立した予測因子であり、白質病変体積は認知機能障害と相関した。同様の結果は最近のSMART-MR（Second Manifestations of Arterial Disease-Magnetic Resonance）研究でも示されている。本研究では565名の症候性アテローム硬化症患者において、自覚病変の重症度とその進行程度が皮質容積の減少、脳室拡大と相関していた。また、登録時のラクナ梗塞数はその後の脳萎縮と相関し、その増加は全脳容積および皮質容積の減少と関連していた。血管病変と変性病態の関係は複雑であるが、血管性認知障害や皮質下血管性認知症における脳萎縮は偶然の産物ではないようである。

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