Vascular cognitive impairment (VCI) remains a challenge of integrating what we know with evaluating what we do to catalyze progress.1 Hachinski has suggested that we optimize knowledge acquisition and application in stroke and VCI by “The Triple T Approach” of transdisciplinary, translational, and transactional interchanges.1 Our understanding of VCI continues to evolve and cannot be taken in isolation of Alzheimer disease (AD) as important overlap and potential synergy may exist for the two disorders. In relation to VCI, select studies published in 2007 have shown that: (1) Knowledge of post-stroke cognitive impairment and its long-term development is poor as illustrated by the nonlinear time course of memory dysfunction after stroke2,3; (2) A history of stroke symptoms without a history of stroke or TIA (so-called “whispering strokes”) is associated with cognitive impairment which is increased with the occurrence of each additional modifiable cardiovascular risk factor4; and (3) For cognitive impairment, no dementia (CIND), and mild cognitive impairment (MCI), a history of previous stroke may increase the risk of dementia.5 In this update we review advances in VCI that took place in 2007.

Neuropathology

Based on 148 autopsy subjects of the Rush Memory and Aging Project, Schneider et al reported that after controlling for cortical infarcts and AD pathology, subcortical infarcts increased the odds of dementia by almost 4 times, reduced cognitive function by more than a third of a unit (P<0.05), and interacted with AD pathology to worsen working memory (P=0.02).6 The importance of subcortical infarcts in dementia risk and severity had previously been shown in the Nun Study. In a hospital-based sample of 43 autopsy patients from Geneva, Switzerland with a Clinical Dementia Rating Scale (CDR) within about 3 months before death, Braak III stage AD, and no history of stroke or other central nervous system disorders, Kovari et al showed that cortical microinfarcts, but to a lesser degree periventricular demyelination, contributed to cognitive decline in these persons at high-risk for dementia.7 Previously, Chui et al noted in a convenience autopsy sample enriched with subcortical ischemic vascular disease (n=79) that hippocampal sclerosis (HS) was a common yet unexpected finding; APOE e4 was associated with cerebral amyloid angiopathy; and cerebral vascular disease parenchymal pathology score (CVDPS) and HS contributed to cognitive impairment.8 However, in patients with advanced AD Braak and Braak pathology stage, the effects of CVDPS and HS were overwhelmed by AD stage.8

The neurovascular unit (NVU) may play an important role in linking AD and VCI through vascular dysfunction. For example, NVU-related cerebral blood flow regulation and blood brain barrier transport could impair A-beta amyloid (AB) clearance leading to increased brain forms of soluble and fibrillary AB. Furthermore, NVU-regulated reduction of cerebral perfusion could potentiate brain inflammation lesions.9,10

Cardiovascular Risk Factors

Lifestyle Cardiovascular Disease Risk Factors

Lifestyle factors may confer risk for cognitive impairment.11 These factors could raise risk for VCI or AD. In the Washington Heights and Inwood Columbia Aging Project, Scarmeas et al have shown that adherence to the Mediterranean diet (ie, high intake of cereals, fruits and vegetables, legumes, fish, and unsaturated fatty acids and low intake of saturated fatty acids, dairy products, meat, and poultry) may not only lower risk for AD but may also lower mortality in AD.12 Recent publications concerning other lifestyle factors and cognitive impairment are listed in supplemental Table I, available online at http://stroke.ahajournals.org.

Medical Factors

Neuronal damage in brain inflammation may be a common pathway which leads to cognitive impairment, stroke, AD, and Parkinson disease.13 In the Framingham Study a panel of inflammatory biomarkers in observational cross-sectional study has been associated with greater brain atrophy which is more pronounced in men and older persons,14 and interleukin 1 or tumor necrosis factor alpha-a may be a marker of future risk of AD.15 Low-grade inflammation has been suggested as a risk factor for silent cerebral infarcts,16 a factor which raises risk for dementia. Nonsteroidal antiinflammatory drugs (NSAIDs) do not seem, however, to reduce dementia or AD risk.17,18 It has been suggested, though, that NSAID use in midlife rather than later life could prevent cognitive decline.
in older adults, especially in those with one or more copies of APOE e4.19 Other recent publications concerning medical risk factors and cognitive impairment are listed in supplemental Table II available online at http://stroke.ahajournals.org.

Cerebral Amyloid Angiopathy and Brain Microbleeds
Greenberg et al have recently described cases of cerebral amyloid angiopathy (CAA)-related inflammation.20,21 These patients may have cognitive/behavioral deterioration, seizures, headaches, T2-hyperintensities on MRI, and neuropathologic evidence of CAA-related vascular inflammation. The T2 hyperintensities may be asymmetric, extend to the subcortical region, and overlay gray matter with signal properties consistent with vasogenic edema. APOE e4/e4 genotype may be present. Patients may respond to immuno-suppressant treatment. Vascular and brain amyloid load may be detected by the carbon 11-labeled Pittsburgh Compound B (PiB) and positron emission tomography (PET).

Seo et al suggest that the number of cerebral microbleeds as diagnosed by MRI study may be independent predictors of cognitive impairment in multiple domains and severity of dementia.22 Microbleeds have been associated with lacunar infarcts, hemorrhages, white matter changes, and hypertension and withBinswanger disease, mild cognitive impairment and AD.

Migraine: A Threat to Cognition?
Migraine is a disorder that could be a threat to cognition as active migraine with aura has been linked to increased risk of such conditions as ischemic stroke, major cardiovascular disease, and myocardial infarction in women and has been associated with a significantly increased risk of hypertension, hyperlipidemia, and elevated Framingham risk scores.23 Recently, migraine has been shown to have other vascular linkages including neurovascular dysfunction as manifested by altered functional arterial properties and signs of retinopathy24,25 and obesity.26 Somewhat unexpectedly, the Baltimore Epidemiologic Catchment Area Study reported recently that migraineurs, specifically those with aura, had less decline in domains affected by cerebral small vessel disease.27 These patients may have cognitive/behavioral deterioration, seizures, headaches, T2-hyperintensities on MRI, and neuro-pathologic evidence of CAA-related vascular inflammation. The T2 hyperintensities may be asymmetric, extend to the subcortical region, and overlay gray matter with signal properties consistent with vasogenic edema. APOE e4/e4 genotype may be present. Patients may respond to immuno-suppressant treatment. Vascular and brain amyloid load may be detected by the carbon 11-labeled Pittsburgh Compound B (PiB) and positron emission tomography (PET).

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Women and Cognition
Rocca and colleagues at the Mayo Clinic have shown in observational study that both unilateral and bilateral oophorectomy preceding the onset of menopause is associated with increased risk of cognitive impairment and dementia with an age-dependent effect (increased risk at younger ages) and postulate a possible critical age window for neuroprotection.28 Perioperative treatment of women with 17 beta-estradiol in a small clinical trial has not shown to improve cognitive outcomes, however, in postmenopausal cardiac surgery patients.29

Treatment
788 patients with probable vascular dementia were randomized to receive galantamine or placebo and were evaluated on the primary efficacy measures of the Alzheimer’s Disease Assessment Scale-Cognitive subscale (ADAS-cog11) and the Alzheimer’s Disease Cooperative Studies-Activities of Daily Living Inventory (ADCS-ADL) total score.30 After 26 weeks, there was improvement in cognition, including executive function, favoring the galantamine treatment group, good safety and tolerability, but no major difference in activities of daily living between treatment groups. In a recent pooled data analysis of 19,501 subjects, Birns et al concluded that blood pressure lowering may have a heterogenous effect on different aspects of cognition.31 Large-scale controlled trials in which blood pressure lowering agents are administered with cognitive variables as the primary outcome are needed to determine the effect of this potentially important strategy to preserve cognition.

Leukoaraiosis and CADASIL
Leukoaraiosis may be an important predictor of cognitive decline in domains affected by cerebral small vessel disease.32 Furthermore, confluent white matter abnormalities on MRI may be a predictor of progression of volume of white matter lesions,32 and white matter lesion rate of progression may be greater in deep white matter and in anterior brain regions.33 Endothelial dysfunction has been implicated as a mechanism underlying leukoaraiosis,34,35 and these changes may be related to extent and spatial location in common forms of cognitive impairment.36 Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary microangiopathy with white matter lesions on MRI in which lacunar infarction load has been has been associated with cognitive dysfunction and disability.37,38 Brain parenchymal fraction, a marker of cognitive and motor disability in CADASIL, is predicted by age, mean apparent diffusion coefficient, and volume of lacunar lesions suggesting that brain atrophy is related to both consequences of lacunar lesions and widespread micro-structural brain changes outside lacunar lesions in CADASIL.39 Cholinergic neuronal impairment has been noted previously in CADASIL and provides a rationale for cholinomimetic therapy in subcortical forms of VCI.

Neuroimaging
Tractography
One of the major limitations of imaging in VCI is the poor correlation between lesion volume and cognitive deficit. The consequences of lesion location can fairly readily be assessed when gray matter structures are affected. In the very common context of white matter lesions, however, this becomes more difficult as the anatomy of most fiber tracts (hodology—the science of connectional anatomy) is not well known. Even when they are known it is virtually impossible to determine which tracts a lesion may be affecting and the extent to which the tracts may be damaged by inspecting an MRI scan. The problem becomes more complex with lesser degrees of ischemic damage leading to areas of leukoaraiosis, rather than
completed infarcts. The lesions of leukoaraiosis are not homogenous and within areas of similarly abnormal signal on MRI there may be a great variety of degrees of damage, some of which do not necessarily greatly affect function.

Over the past 2 years there has been expansion in the use of diffusion tensor imaging (DTI) to perform tractography whereby fiber pathways can be imaged and which may be important to our understanding of VCI. For example, Yamada et al have demonstrated the anatomy of the thalamocortical projections, and others have demonstrated a second indirect pathway running through the inferior parietal lobe lateral to the traditionally recognized arcuate fasciculus connecting Broca’s and Wernicke’s areas which may explain the variable features of conduction aphasia. Other tracts demonstrated include the dorsal parietofrontal network for spatial orientation and praxis, the limbic network for memory and emotion, transcallosal connections, and ventral occipitotemporal networks for face and object recognition. Furthermore, the technology permits some quantitative assessment of tract integrity.

An early example of the quantitative assessment of tract involvement was the work by Konishi et al correlating stroke severity and outcome in lenticulostriate infarcts with the degree of involvement of the corticospinal tract. Cognitive studies as yet are limited but an elegant report by Yamada et al clearly shows quantifiable damage to the arcuate fasciculus in conduction aphasia. A number of disconnection syndromes have also been studied in this way with correlation between the neuropsychological deficit and affected tracts. Other data relating cognitive changes to tractography are so far few, but this technique promises expansion in hodology with the ultimate promise of standardized 3D hodological atlases.

Individual patients’ lesions might then be projected onto the analysis, offering a clearer understanding of their physical and cognitive deficits and could help determine prognosis and predict the response to and hence selection for treatment.

The potential for these technologies to influence selection for treatment is illustrated by the use of a rating scale for the cholinergic pathways in AD mixed with considerable leukoaraiosis. Although this does not use tractography, and is instead a semiquantitative visual rating scale based on the published anatomy of the cholinergic pathways as determined from immunohistochemistry, the Cholinergic Pathways Hy-PER-intensities Scale (CHIPS) correlates better with cognitive status than does total volume of leukoaraiosis. Interestingly, in a population of patients with probable or possible AD with considerable amounts of leukoaraiosis, those patients with more cerebrovascular involvement of cholinergic pathways responded better to cholinergic drugs. This process could then be extended to other pathways either in this way or through tractography. It is possible to speculate that involvement of extrapyramidal systems could be quantified in a way that might predict responsiveness to L-dopa and of those pathways involved in depression to antidepressants etc.

Fractional Anisotropy

Also in the field of DTI, there have been developments in fractional anisotropy (FA). Early reports date back to 1999 when decreased FA was identified in leukoaraiosis. This work was subsequently extended to show that normal appearing white matter in patients with leukoaraiosis had decreased FA and that this correlated with impaired executive function. The same phenomenon was then identified in the normal elderly with normal standard MRI scans. Recent studies have confirmed these findings and established that FA is a more sensitive tool for the detection of white matter damage affecting cognition than standard sequences including FLAIR. Changes in FA are also increased in those with APOE E4 and they correlate with spectroscopic measurement of N-acetyl aspartate (a marker of neuronal tissue). These findings imply that measures of FA rather than standard volume measurements are more sensitive to changes in the white matter. Given the slow rates of progression seen in leukoaraiosis in all but advanced disease, this technology may offer a surrogate for detecting treatment effects ahead of current standard imaging and neuropsychological changes. That decreased FA is seen in normal aging without visible leukoaraiosis raises the prospect of identifying the holy grail of VCI, the “brain-at-risk” where treatment may prevent cognitive decline. Patients with AD also demonstrate decreased fractional anisotropy. Some part of this correlates with focal cortical atrophy suggesting that there may be an early vascular component in AD as well.

Conclusion

Advances in our knowledge of VCI are being led by new developments in the understanding of cardiovascular risk factors and the role of these factors in AD, CADASIL as a model for subcortical VCI, and neuroimaging such as tractography and DTI which help elucidate lesion location and brain integrity in cognitive impairment. These advances emphasize the need for transdisciplinary, translational, and transactional approaches to better understand VCI.

Disclosures

Philip B. Gorelick: Consultant to Bayer, Boehringer Ingelheim, BrainsGate, Johnson and Johnson, diaDexus, Myriad, Pfizer, TAP; Speaker’s Bureau for Boehringer Ingelheim.

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Key Words: neuroimaging ■ risk factors ■ treatment ■ vascular cognitive impairment
Advances in Vascular Cognitive Impairment 2007
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*Stroke*. 2008;39:279-282; originally published online January 10, 2008;
doi: 10.1161/STROKEAHA.107.509570

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/39/2/279

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