Advances in Vascular Cognitive Impairment 2006

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Vascular cognitive impairment is common and represents a spectrum of cognitive dysfunction associated with stroke and cardiovascular risk factors which may be slight, moderate or severe.1 Recently and as a major advance, the National Institute of Neurological Disorders and Stroke—Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Working Group published clinical and research standards for the description and study of vascular cognitive impairment.2 In this update we report advances in vascular cognitive impairment in the following areas: clinical trials and treatment, new risk factors, white matter disease, and genetics.

Clinical Trials and Treatment: Blood Pressure and Hyperglycemia

Cardiovascular risk factors such as blood pressure elevation and hyperglycemia are prime targets for clinical trial study because they are believed to cause negative effects on brain structure and cognitive function and may even influence risk of Alzheimer disease (AD).3 Results of recently published observational epidemiological studies have fueled controversy in relation to the role of blood pressure on cognition because some studies such as the Honolulu Asia Aging Study4 and Cache County Study5 suggest that antihypertensive therapy may reduce risk of dementia and cognitive decline or reduce incidence of AD, respectively, whereas the Religious Orders Study6 did not find an association between blood pressure and risk of AD or cognitive decline. Meta-analysis of patients with cardiovascular and/or cerebrovascular disease who received blood pressure–lowering treatment show a trend toward prevention of dementia and/or cognitive decline;7 however, a systematic analysis of 3 studies comprising 12,091 patients with hypertension who were treated with either medication or lifestyle strategies for at least 6 months show no evidence that blood pressure–lowering prevents dementia or cognitive impairment.8 Lack of definitive results in some of these trials may be explained by insufficient power to detect treatment effects, measurement error in cognitive end points, variation in treatment effects between different classes of antihypertensive agents, bias attributable to missing data, variation in baseline factors, and cognitive function status at entry.7 The disparate results suggest the need for well-designed trials and primary hypotheses to determine whether blood pressure–lowering is an important intervention for maintaining cognitive vitality in those with or without major cardiovascular disease.9

Glucose and insulin may have important effects on cognitive function. Insulin receptors may be found in high concentration within the limbic system and influence the firing of hippocampal neurons and enhance neuronal glucose uptake.9 Chronic hyperinsulinemia, however, may reduce insulin transport into the brain and lead to inhibition of \( \tau \) phosphorylation, promotion of \( \alpha-B \) release from intracellular to extracellular compartments, or expression of insulin degrading enzyme, a major protease responsible for \( \alpha-B \) clearance.10,11 Furthermore, the receptor for advanced glycation end products (RAGE), a cell surface receptor implicated in vascular disease and neurodegeneration, may be reduced in AD.12 A recently published randomized, double-blind trial in type 2 diabetics receiving metformin monotherapy compared add-on therapy with either rosiglitazone or glyburide among 145 subjects.13 Cognitive testing was carried out at baseline and at 24 weeks using the Digit Symbol Substitution Test, the Rey Auditory Verbal Learning Test, and the Cambridge Neuropsychological Test Automated Battery. This exploratory study showed that similar and statistically significant cognitive improvement was noted with either add-on treatment and was correlated with the degree of improvement in fasting plasma glucose.

Concern has been raised in relation to possible adverse cognitive effects in diabetics who experience tight control of glucose. In type 1 diabetics, tight control of glucose did not appear to impair long-term cognitive function according to results from the Diabetes Control and Complications Trial (DCCT).14

New Risk Factors: Lipoprotein-Associated Phospholipase A2 and Metabolic Syndrome

Inflammatory markers such as high-sensitivity C-reactive protein and interleukin-6 have been implicated in conferring risk of cognitive impairment.15–17 A new marker, lipoprotein-associated phospholipase A2 (Lp-PLA2), also may confer risk of cognitive impairment.18 Lp-PLA2 is from a family of enzymes which hydrolyze phospholipids, is upregulated in atherosclerosis, predominantly binds to LDL-cholesterol, and raises risk of stroke and coronary heart disease by several-
fold. In a case-control design from the Rotterdam Study, a prospective population-based cohort, it has been shown that Lp-PLA2 is associated with risk of dementia independent of cardiovascular and inflammatory factors. Metabolic syndrome, another disorder which is believed to be one of the inflammatory diseases, may be associated with silent brain infarction which may increase risk of cognitive impairment. Inflammation may be an important and treatable cause for cognitive impairment.

Genetics

Genetic host contributions to blood vessel susceptibility to hypertensive damage, etc, were shown by the 1998 NHLBI Twin Study, which revealed 71% heritability for leukoaraiosis and by the Framingham and GENOA studies in 2004. These observations have been extended over the past year. The Framingham Heart Study presented the first genome wide linkage analysis for leukoaraiosis and identified one peak logarithm of the odds score of 3.69, indicating significant evidence of linkage, on chromosome 4p. This region is not one where the known stroke-related genes are situated and there is no clear candidate gene here although there are a number of aging and mitochondria-related genes. An additional possible locus of logarithm of the odds 1.78 was observed on chromosome 17.

A mutation in the \textit{COL4A1} gene, which encodes for basement membrane type IV \alpha 1 collagen, has been identified that causes intracerebral hemorrhage in mice and which seems, in one reported family, to be associated with extensive leukoaraiosis, microhemorrhages, retinal arteriolar tortuosity and possibly fatal intracerebral hemorrhage in humans. This adds to the list of single-gene inheritable conditions associated with leukoaraiosis and raises the possibility that other genes encoding structurally important proteins might contribute to small-vessel cerebrovascular disease.

Leukoaraiosis: Etiology

There has been some debate as to whether periventricular and deep subcortical leukoaraiosis share the same etiology. The MRC Cognitive Function and Ageing Study used MRI of postmortem brain slices to identify leukoaraiosis and then studied these areas histopathologically and with molecular markers of hypoxia. There was clear evidence of chronic hypoxia in areas of leukoaraiosis and some suggestion that hypoxic changes in periventricular leukoaraiosis may be less pronounced and that these lesions are associated with ependymal loss. Whether this will translate into different risk factors and management remains to be established. This has also been investigated from the genetic point-of-view. Henskens et al looked at a number of previously recognized genetic associations and assessed their relationship to periventricular and subcortical leukoaraiosis, measured using a semiquantitative scheme. Periventricular leukoaraiosis was not affected by RAS or NOS3 (eNOS) polymorphisms. Subcortical leukoaraiosis was not associated with ACE I/D and the AGT M235T polymorphisms but was associated with AGTR1 A1166C and the NOS3 G894T polymorphisms, the AGTR1 C allele being protective and the NOS3 T allele apparently increasing susceptibility to leukoaraiosis after correction for age, diabetes and blood pressure. Some of the findings are in contradiction to previous studies, and the authors make the crucial point that accurate phenotyping is essential. Taken in conjunction with the MRC data, it may be that the mechanisms and genetic risk factors for deep subcortical and periventricular leukoaraiosis are not the same, with the implication that studying them together may prove misleading.

Leukoaraiosis: Progression and Cognitive Consequences

Having established the increasing knowledge about factors that lead to the development of leukoaraiosis, there arises the question of its importance. Early data suggested it was of little importance although we now know this to be incorrect, the error occurring through combining exquisitely sensitive imaging techniques with inappropriate and insensitive neuropsychology.

The Framingham study compared leukoaraiosis, divided categorically into “large” (more than 1 SD above age-predicted mean) and everyone else, with cognitive impairment measured in a variety of domains, in 1820 nondemented subjects with a mean age of 61. They found clear impairment in attention, planning, activity initiation, visual organization and new learning with increased leukoaraiosis, whereas verbal memory did not differ.

Several population-based studies, these being the Cardiovascular Health Study (CHS), Rotterdam Scan Study (RSS), Austrian stroke prevention study (ASPS), and PROSPER along with a smaller study from Denmark, have also

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<th>Subject Demographics, Rates of Change of Leukoaraiosis and Cognitive Deficits for Those Studies With Longitudinal Data</th>
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MMSE indicates Mini-Mental State Examination; WAIS, Wechsler Adult Intelligence Scale.
recently reported on the progression of leukoaraiosis and its cognitive correlates. Combined, the studies provide data on 3660 subjects aged 60 to 90 (Table). Leukoaraiosis was only scored in CHS and RSS but quantitative data on progression are available from the others, the difference between the mean rate in ASPS compared with PROSPER and the Denmark study possibly being attributable to age as more rapid progression is seen with increasing age. The PROSPER study subdivided the areas into deep white matter (0.14 mL/year) and periventricular white matter (0.54 mL/year) suggesting more rapid progression of periventricular disease. Cognitive correlates of leukoaraiosis were universally found, and these broadly correspond to the subcortical pattern of impaired frontal and executive functions increasingly recognized with leukoaraiosis. Cognitive decline was 4 times faster in those with the greatest progression of leukoaraiosis. Overall, the changes were modest but may underestimate rates of change in those at greatest risk because there was a pronounced tendency for those with greater cognitive impairment to decline assessment, and in those studies where factors predicting rate of decline were measured, greater disease (leukoaraiosis or cognitive) at entry predicted more rapid increases in leukoaraiosis and cognitive decline. In ASPS, extensive leukoaraiosis at entry doubled the rate of atrophy. These data imply that trials of treatment aimed at slowing progression of leukoaraiosis might best be focused on the more severe groups in order to increase sensitivity and reduce sample size and study duration.

Leukoaraiosis: Effect of Progression Rates on Future Study Design

The developments in clinical trials and risk factors over the past year coupled with the new data on the progression of leukoaraiosis and its cognitive consequences are important because, taken together, they inform potential future study design. Given the relatively modest progression of leukoaraiosis and cognitive decline over periods of \( \approx 5 \) years, it is not surprising that the outcomes from shorter-term randomized studies are negative or marginal. To obtain meaningful results in pure vascular cognitive impairment, it may be better to focus on those at greatest risk of more rapid progression, ie, those who already have a greater burden of disease. It may even prove to be necessary to select cases according to whether the bulk of the disease is periventricular or deep subcortical. This may not apply in studies looking at the whether the bulk of the disease is periventricular or deep subcortical. This may not apply in studies looking at the mean rate of periventricular or deep subcortical. This may not apply in studies looking at the mean rate of stroke and cardiovascular disease risk factors. Stroke. 2005;36:875–879.


**Key Word:** vascular cognitive impairment