Diagnosis of vascular cognitive impairment (VCI) or vascular dementia (VaD) is highly dependent on operational definitions. Among 480 cases of incident dementia in the Cardiovascular Health Study (CHS) Cognition Study, Lopez et al demonstrated how findings from brain imaging and choice of diagnostic criteria influence the classification of VaD. As shown by previous investigators, the number of cases classified as VaD increases with the availability of imaging. Furthermore, the widely-used NINDS-AIREN criteria (42 probable VaD) are more conservative than the DMS IV (62 VaD) or California ADDTC criteria (117 probable VaD). In the CHS cohort, several baseline MRI findings (in addition to history of stroke) were identified as risk factors for incident VaD: white matter hyperintensities (WMH), number of MRI infarcts, and ventricular size. Increased incidence of Alzheimer disease (AD) was also increased by the severity of coronary and peripheral atherosclerosis. Thus, MRI or systemic measures of CVD may offer important surrogate markers for VCI.

VaD is purported to be more common than AD in Asia. In a study of 34 807 persons, aged 65 or older, living in several Chinese communities, Zhang et al reported a prevalence of 4.8% for AD and 1.1% for VaD. These results suggest that the prevalence of dementia subtypes in China is similar to Western countries. It should be noted, however, that the application of NINDS-AIREN criteria and the absence of brain imaging may underestimate the extent of underlying CVD.

Costs related to VCI for society and individuals have been examined. According to 2 studies, annual utilization of health care resources and primary caregivers are higher for VaD than AD. In the CHS cohort, median survival from dementia onset to death was shorter in VaD (3.9 year) than in AD (7.1 years) and cognitively normal controls (11.0 years). This is not surprising, because VaD would be associated with higher cardiovascular mortality.

The role of inflammation, infection, and antioxidants have been explored. In the Rotterdam Study levels of fibrinogen, but not C-reactive protein, were associated with an increased risk of AD and VaD. In a Japanese case-control study, antibodies against Chlamydia pneumoniae were found more often in VaD than in AD. In the Canadian Study of Health and Aging, subjects reporting any antioxidant vitamin–use at baseline showed a significantly lower risk for incident VCI, but not dementia or AD. These data are intriguing but preliminary.

**Neuroimaging**

Associations between WMH, neuropsychological impairment and brain atrophy have been studied. The prospective, population-based Rotterdam Scan Study observed periventricular WMH, generalized brain atrophy, and brain infarcts on MRI to be associated with steeper decline in information processing speed and executive function during 5.2 years-mean follow-up. In a clinical study on 69 patients with dementia, those with severe WMH displayed greater executive/visuospatial impairment relative to memory/language disabilities, whereas those with milder white matter abnormalities displayed relatively more memory/language disabilities. In a sample of 50 AD, 13 mixed AD/subcortical vascular dementia (SVD) and 77 cognitively-intact controls, WMH correlated with cortical gray matter atrophy, but not with hippocampal or entorhinal atrophy. Assuming that medial temporal atrophy is a marker for AD, whereas WMH is a marker for SVD, these findings suggest AD and SVD are independent processes and that both contribute to cortical gray matter atrophy. Thus, WMH appears to contribute to cognitive decline and loss of brain volume in the elderly.

**Pathology**

Heterogeneity and overlap pose ongoing challenges for the pathological classification of VaD. Among 175 autopsied VaD cases, only 49 (28%) were classified as “pure” VaD (ie, with only 1 type of vascular brain lesion and without AD pathology). Of these, 36 had small vessel disease, 7 large vessel disease, and 6 hypoxic-hypoperfusion injury. The remaining 126 cases (72%) showed, in addition to Alzheimer pathology, a mixture of small vessel disease, large vessel disease, and hypoxic-hypoperfusion injury. The influence on mixed pathology was illustrated further in the Honolulu-Asia Aging Study, where the presence of cerebrovascular lesions more than doubled dementia frequency in men with sparse neuritic plaques. Gold et al related lacunar and microvascular pathology to cognitive status in 72 elderly individuals without significant neurofibrillary tangles or macrovascular lesions. In a multivariate model, cortical microinfarcts, and thalamic/basal ganglia lacunes explained 22% of variance; amyloid deposits and microvascular pathology 12%; whereas...
deep white matter lacunes were not significant contributors. These data contribute to a growing database that may one day enable weighting of type, severity, and location of microvascular pathology to cognitive impairment.

Severity of memory impairment and hippocampal atrophy have been correlated with neuropathology. Zarow et al27 reported numbers of CA-1 neurons to be lower in subjects with AD and hippocampal sclerosis compared with subcortical vascular dementia. Numbers of CA-1 neurons correlated with memory scores and MRI-derived hippocampal volumes irrespective of etiological diagnosis. Thomas et al29 observed a correlation between memory impairment and parenchymal amyloid load in both AD and VaD, particularly for AB42 accumulation in the entorhinal cortex. Loss of CA-1 neurons, and perhaps medial temporal lobe accumulation of amyloid, figure as an important determinant of memory impairment in both AD and VaD.

During the past decade, CVD has been associated with AD as well as VaD. In a retrospective review of 1054 neuropathology cases, Honig et al19 found no associations between small vessel cerebrovascular disease (arteriosclerosis) and plaques and tangles. However, large-vessel cerebrovascular disease (atherosclerosis) was strongly associated with an increased frequency of neuritic plaques. Jellinger and Attems20 noted a higher frequency of vascular pathology and cerebral amyloid angiopathy in AD versus controls (57.34% versus 33.2%; 94.1% versus 33.3%, respectively). Thus, AD may be associated with 2 types of vascopathology: large vessel atherosclerosis, as well as amyloid angiopathy.

The status of the cholinergic system may differ according to VaD subtype. Perry et al21 reported decreased cholineacetyltransferase levels in temporal cortex in AD and mixed AD/VaD, but not pure VaD. In a study ofBinswanger-type VaD,22 as in previous studies of CADASIL, subinsular cholinergic fibers were diminished despite preservation of neurons in the nucleus basalis. These findings lend biochemical rationale for treatment at least of the Binswanger and CADASIL subtypes of VaD with cholinesterase inhibitors.

Treatment

Roman et al23 reported a combined analysis of the 2 largest randomized, double-blind, placebo-controlled, 24-week studies involving 1219 patients, and Passmore et al24 conducted a meta-analysis of 10-clinical trials for donepezil. The donepezil versus placebo was studied in 230 patients with subcortical VaD.26 At 52 weeks, the Sandoz Clinical Assessment Geriatric scale 5-point variation (primary outcome measure) did not differ significantly between the groups. However, cognitive and global deterioration appeared to be less frequent in the nimodipine group, whereas dropouts and adverse events were more common in the placebo group. Confirming previous results, the safety analysis of this study shows that in this high-risk population, nimodipine might protect against cardiovascular comorbidities.

CADASIL

Prevalence was calculated for definite CADASIL based on population figure from the 2002 national census in west Scotland.27 Twenty-two individuals from 7 pedigrees with confirmed CADASIL were identified, yielding a prevalence of 1.98 per 100 000. An additional 37 individuals were predicted to be carriers of the Notch3 mutation, yielding a probable mutation prevalence of 4.14 per 100 000 adults.

The location of Notch3 mutations may differ geographically. In 125 unrelated German CADASIL patients with biopsy-proven disease, Peters et al28 detected 54 distinct mutations in 96.0% of the patients. Almost 90% of mutations could be detected within a few exons (exons 2 to 4). In contrast, in 28 unrelated CADASIL families from central and south Italy, the highest mutations rate was found in exon 11 (21%), and only 18% were in exon 4.29 Tang et al30 report the first known Taiwanese family affected by CADASIL (Arg332Cys at exon 6). The results suggest that limited scanning of exons 3 and 4 is inadvisable in CADASIL cases of Italian origin. Moreover, if genetic screening is negative in highly suspected cases, skin biopsy is advised.

Several studies in transgenic mice point to possible pathological changes associated with CADASIL. Dubroca et al31 observed significant decreases in flow-induced dilation. Lacombe et al32 noted reduced responses to hypercapnia and acetazolamide, higher cerebrovascular resistance during hypotension, and rightward shift of CBF autoregulation curves. No significant impairment in dynamic cerebral autoregulation or carbon dioxide reactivity was found in humans with CADASIL using transcranial Doppler ultrasound.33 The animal data suggest early impairment of autoregulation, perhaps attributable to decreased relaxation or increased resistance of cerebral vessels, which has not yet been detected in humans with CADASIL, at least using transcranial Doppler.

References


Key Words: vascular cognitive impairment.
Advances in Vascular Cognitive Impairment 2005
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Stroke. published online January 12, 2006;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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