Vascular Dementia: 
The Beginning of a New Era

Our concepts of vascular dementia (VaD) have been evolving rapidly during the past decade, and have broadened beyond the traditional understanding of VaD as being only a multi-infarct dementia (MID). It is now recognized that there are a broad range of cerebrovascular syndromes that can produce VaD, including strategic infarcts, subcortical VaD, and amyloid angiopathy. There has been emerging interest in the state of vascular cognitive impairment not dementia (vascular CIND) where it may be possible to intercede in treating vascular risk factors and stroke mechanisms before dementia becomes fully manifest. Indeed, there is evidence that treating vascular risk factors in asymptomatic individuals can lower the risk of developing dementia. Finally, the acetylcholinesterase inhibitors are emerging as a treatment option for the symptoms of VaD, with clinical trial evidence showing benefits on cognition, behaviour and functional disability.

by Inge Loy-English, MD, FRCPC and Howard Feldman, MD, FRCPC

Epidemiology
In the Canadian Study of Health and Aging (CSHA), vascular dementia (VaD) was described as the second most common cause of dementia, affecting 1.5% of the population older than 65 years.1 In a subsequent study, known as A Canadian Cohort Study of Cognitive Impairment and Related Dementias (ACCORD), 8.7% of individuals referred to dementia clinics in Canada were diagnosed as having VaD.2 In addition to the patients who are clearly demented as a result of cerebrovascular disease, there also are those who have vascular cognitive impairment (VCI) without dementia. This group makes up a further 2.6% of the population in the CSHA,3 and accounts for about 18% of those in the ACCORD study considered cognitively impaired but not demented.2

The risk of VaD increases with age—though less steeply than in Alzheimer’s disease (AD)—and generally is found to be more prevalent in men than women.4 The prevalence of dementia following a stroke is roughly 25%.5 The magnitude of the burden of cerebrovascular disease and its impact on cognitive function represents a huge challenge in an aging society.

Classification and Clinical Features
The definitions of VaD have been changing over the past few years. In VaD caused by cerebrovascular disease, early descriptions centered on multiple cortical and subcortical infarcts. In this type of VaD, the onset and worsening of the cognitive state is linked temporally to an episode of stroke or a transient ischemic attack (TIA). Current definitions of VaD describe it as a heterogenous disorder, as symptoms and signs are related to the cortical or subcortical area injured by the stroke. The pattern of deterioration usually is step-wise, and there are obvious focal neurologic deficits related to previous strokes.

The Hachinski Ischemic Score was developed to help differentiate between VaD and AD (see Table 1).6 A scale is used in which

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various features considered characteristic of VaD are assigned a value of 1 or 2. A score over 7 is diagnostic of VaD/multi-infarct dementia (MID), a score between 4 and 7 is diagnostic of mixed dementia and a score less than 4 is diagnostic of AD or other nonvascular causes of dementia.

Figure 1 presents examples of vascular disorders that are associated with both VCI and VaD:

**MID.** The concept of MID (Figure 1A) has gradually been expanded to include dementia associated with a larger variety of cerebrovascular disorders.

**Subcortical VaD** includes the termsBinswanger’s disease and “état lacunaire,” and is primarily characterized by an insidious onset in over 50% of patients, rarely with a clear stepwise progression. While having focal neurologic features on examination (e.g., subtle unilateral or bilateral weakness, Babinski signs, sensory deficits, dysarthria), patients often will not have a clear history of a TIA or stroke. Patients also may have an atypical gait (e.g., “marche-a-petit-pas”), resulting from frontal-subcortical damage. Cognitively, there is prominent frontal dysfunction with difficulty in executive functions, including planning, sequencing and organization. The memory impairment in VCI and VaD often is mild, especially compared to AD, with more impaired retrieval and better preserved recognition memory. Computed tomography (CT) scans and, more effectively, magnetic resonance imaging (MRI) show extensive ischemic lesions and lacunar infarcts in the deep and superficial white matter and grey matter bilaterally (Figure 1B).

**Strategic infarcts** are an increasingly recognized and important category of VCI and VaD. While in other types of VaD it is estimated that patients need a cumulative volumetric damage to 100 cubic centimetres of brain to produce dementia, in strategic infarct dementia, the required volume may be only one tenth that amount. Examples of strategic lesions include thalamic, hippocampal and dominant angular gyrus lesions (Figure 1C). The clinical cognitive impairment depends entirely on the location of the strategic lesions. In the example of bilateral thalamic infarcts, there may be a dense amnestic syndrome associated with bilateral upgaze palsies. A severe dominant angular gyrus lesion can produce the classic Gerstmann’s syndrome of right-left disorientation, finger agnosia, dyscalculia and agraphia. It is important to recognize the phenotype of the single strategic-area lesion, to facilitate early diagnosis and treatment.

**Global cortical hypoperfusion** post cardiac arrest is another subtype of VaD (Figure 1D).

**Hemorrhagic disorders** (Figure 1E) also are subtypes of VaD (e.g., cerebral amyloid angiopathy, or following subarachnoid hemorrhage).

**CADASIL.** There also are rare hereditary causes of multiple strokes leading to dementia. The recently described entity of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is becoming increasingly recognized as a cause of otherwise unexplained subcortical VaD in young and middle-aged patients (Figure 1F).

It is worth emphasizing that any of the above subtypes of VCI/VaD can coexist with AD, producing a mixed dementia. Mixed dementia of this type has been reported to account for 18.7% of all dementias diagnosed in the ACCORD study.

### Table 1: Hachinski Ischemic Score*

<table>
<thead>
<tr>
<th>Feature</th>
<th>Point Value</th>
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<tbody>
<tr>
<td>Abrupt onset</td>
<td>2</td>
</tr>
<tr>
<td>Stepwise deterioration</td>
<td>1</td>
</tr>
<tr>
<td>Fluctuating course</td>
<td>2</td>
</tr>
<tr>
<td>Nocturnal confusion</td>
<td>1</td>
</tr>
<tr>
<td>Relative preservation of personality</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>1</td>
</tr>
<tr>
<td>Emotional incontinence</td>
<td>1</td>
</tr>
<tr>
<td>History or presence of hypertension</td>
<td>1</td>
</tr>
<tr>
<td>History of stroke</td>
<td>2</td>
</tr>
<tr>
<td>Evidence of associated atherosclerosis</td>
<td>1</td>
</tr>
<tr>
<td>Focal neurologic symptoms</td>
<td>2</td>
</tr>
<tr>
<td>Focal neurologic signs</td>
<td>2</td>
</tr>
</tbody>
</table>

* A score of >7 is suggestive of VaD; a score of ≤4 is suggestive of AD or another nonvascular dementia; a score of 4-7 suggests mixed dementia.


### Diagnostic Criteria

There are three sets of diagnostic criteria currently being used in research settings for VaD: 1) the fourth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV); 2) the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10); and 3) the NINDS-AIREN criteria (NINDS = National Institute of Neurological Disorders and Stroke; AIREN = Association Internationale pour la Recherche et l’Enseignement en Neurosciences). Although they
are not applied rigorously in clinical practice, it is worth considering some of the points of diagnostic emphasis (Table 2). The NINDS-AIREN criteria, which are the most widely used in recent clinical trials, require a temporal relationship with the onset of dementia occurring within three months of a recognized clinical stroke. They also specify that there be neuroimaging confirmation of ischemic lesions to make the diagnosis.

**Treatment**

The fundamental approach to the treatment of VCI and VaD is centered on the prevention of further ischemic cerebrovascular disease. More recently, however, evidence has emerged supporting the use of acetylcholinesterase inhibitors in the treatment of VaD.

**Vascular risk factors:**

- *Hypertension.* Hypertension has long been known to be a risk factor for stroke and VaD, however the effects of treating hypertension on preventing dementia have been elucidated only more recently. The Systolic Hypertension in Europe (Syst-Eur) trial investigated the effects of treatment of systolic hypertension in mid-life. This double-blind, placebo-controlled, randomized controlled trial (RCT) compared the ability of nitrendipine, +/- enalapril and +/- hydrochlorothiazide, with that of placebo to control systolic blood pressure to below 150 mmHg. Results demonstrated a 55% reduction in the incidence of dementia (95% CI, 24%-73%) and a 42% reduction in stroke (95% CI, 17%-60%) with active treatment. There were fewer cases of VaD and AD in the active treatment group.

  In a recent article analyzing all the studies of the effects of treating hypertension on VCI, the authors concluded that decreasing hypertension in the elderly is safe and effective in reducing morbidity and mortality. Angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (especially nicardipine and nitrendipine) have the best supportive evidence with respect to preventing VCI associated with hypertension. There is less evidence to support the use of diuretics and beta-blockers in this regard.

- *Diabetes mellitus.* The association between diabetes mellitus and stroke also is well known, with recent recognition of an association between diabetes and incident cognitive impairment. A recent Cochrane review concluded that there was upwards of a two-fold increase in the risk of cognitive impairment in diabetics compared to the general population. Although the evidence remains uncertain with respect to diabetes treatment...
reducing the incidence of dementia, there is evidence that treating hyperglycemia has a positive effect on cognitive function, at least in the short term.\textsuperscript{15,16} This adds to the clear benefits of treating blood sugars tenaciously to prevent the spectrum of diabetic complications.

d) Stroke. The use of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (i.e., statins) has emerged as a common practice in the secondary prevention of stroke. There have been two recent meta-analyses evaluating the effect of statins primarily on the risk of stroke in patients with coronary artery disease.\textsuperscript{17,18} These analyses showed a reduction in stroke rate of approximately 25\% to 30\% using pooled data.

The recently published Heart Protection Study\textsuperscript{19} investigated the effects of simvastatin on vascular outcomes, including stroke, myocardial infarction (MI) and death. In this double-blind RCT, 20,536 patients were allocated to receive simvastatin or placebo. The risks of stroke, MI and death all were significantly decreased in the active treatment group, however there was no significant benefit of simvastatin on five-year cognitive outcomes.

d) Homocysteine. Homocysteine is a recently identified risk factor for cerebrovascular disease and dementia. It is known from previous studies that there is an independent linear relationship between the risk of TIA, stroke and increasing homocysteine levels.\textsuperscript{20} The treatment for lowering plasma homocysteine levels is felt to be well tolerated: daily supplementation with vitamin B6 (25 mg), vitamin B12 (250 mg to 500 mg) and folic acid (2 mg to 3 mg). While there have been no studies to date looking specifically at the outcomes of lowering homocysteine levels in VCI or VaD, there are currently ongoing studies looking at the role of homocysteine in both reducing the risk of stroke and as a treatment for AD.

Table 2

<table>
<thead>
<tr>
<th>Diagnostic Criteria for Probable VaD</th>
<th>DSM-IV</th>
<th>ICD-10</th>
<th>NINDS-AIREN</th>
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<tbody>
<tr>
<td>Ischemic stroke and hemorrhagic stroke</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Stepwise deterioration required</td>
<td>Yes</td>
<td>No</td>
<td>Yes (or temporal relationship between stroke and dementia)</td>
</tr>
<tr>
<td>Unequal distribution of cognitive defects</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Focal neurologic signs</td>
<td>Yes (or radiographic evidence of significant cerebrovascular disease)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Focal neurologic symptoms</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Etiologic relation of stroke to the disturbance in cognition</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Temporal relation between stroke and dementia onset</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Structural neuroimaging required</td>
<td>Yes (or clinical evidence of significant cerebrovascular disease)</td>
<td>No</td>
<td>Yes: multiple large vessel strokes or multiple lacunes or extensive white-matter lesions or a single, strategically placed lesion</td>
</tr>
</tbody>
</table>

**Treatment with antiplatelet agents.** There has only been a single RCT evaluating the effects of antiplatelet agents in dementia.\textsuperscript{21} In this three-year, single-blind study, 70 patients with MID were randomized to either treatment with acetylsalicylic acid (ASA) 325 mg or an untreated control group. There were significant improvements in cerebral perfusion values and cognitive performance scores for the patients treated with ASA compared to the untreated patients. This study has not been replicated and there have been no studies on the role of other antiplatelet agents (e.g., ticlopidine, clopidogrel, dipyridamole/ASA combinations) or warfarin in VCI or VaD.

**Symptomatic treatment for VaD.** The recognition of cholinergic deficits in VaD and VCI has led to the recent treatment trials with acetylcholinesterase inhibitors. In one double-blind, placebo-controlled study, donepezil was investigated for safety and
efficacy in probable VaD, as defined by the NINDS-AIREN criteria. There was benefit in the 5 mg and 10 mg donepezil groups compared to placebo on the Clinician’s Interview-based Impression of Change (CIBIC-plus; a global assessment measure) and on the cognitive subscale of the Alzheimer’s Disease Assessment Scale (ADAS-Cog; a psychometric assessment).

Galantamine also has been evaluated in a double-blind RCT that included probable VaD and mixed AD-VaD. The group treated with galantamine did significantly better at six months than the placebo group on the CIBIC-plus and the ADAS-Cog.

There have been no published RCTs evaluating the efficacy of rivastigmine in VaD or mixed AD-VaD.

Conclusions

VCI and VaD are a heterogenous group of disorders that are becoming better understood with the advent of better diagnostic criteria and neuroimaging. The phenotypic identification of subtypes of VCI and VaD may allow more targeted therapy in the future. At present, diligent control of vascular risk factors clearly is important in trying to prevent ongoing or increasing ischemic injury. The use of acetylcholinesterase inhibitors in the symptomatic treatment of VaD is emerging as a treatment intervention supported by level I evidence from recent RCTs.

Acknowledgements

The authors gratefully acknowledge Dr. Doug Graeb and Professor Philip Scheltens for contributing the CTs and MRIs used in Figure 1. The capable assistance of Mr. Jacob Grand in the development of this manuscript also is acknowledged with appreciation.

References: