Vascular Concept: Vascular Risk Factors and AD

There is considerable epidemiologic evidence supporting the concept that Alzheimer’s disease (AD) is a multifactorial disorder with a definite vascular contribution. In this article, Dr. Dalziel reviews the role of vascular risk factors in the development and severity of AD.

By William B. Dalziel, MD, FRCPC

Are VAD and AD Separate Entities or Part of a Spectrum?

M.J. Roth in 1955 suggested that vascular Alzheimer’s disease (VAD) and Alzheimer’s disease (AD) were two distinct and separate entities based on distinct etiologies. However, increasingly the concept of dementia embraces the concept of a spectrum with common risk factors and interrelated probably synergistic cerebrovascular and neurodegenerative pathologies.

Cerebrovascular pathology and AD can result in dementia and the prevalence of both diseases increases significantly with age. Vascular pathology on autopsy and neuroimaging is common in AD and in the elderly with normal cognition. Significant cerebrovascular disease (CVD) was found in brain autopsy in AD patients (48%) and in age matched controls with cognitive impairment (33%). In diagnosed VAD patients, 77% had AD pathology. Most patients in the MRC CFAS study (Cognitive Function on Aging Study) had both AD pathology (70%) and vascular pathology (78%).

In the famous longitudinal study of aging and AD, the Nun Study, 47% of the demented patients had AD and 1 or more brain infarcts. For those with AD pathology and lacunar infarcts versus those without infarcts, the odds ratio was 20.7 times more likely that those with infarcts showed clinical signs of dementia while alive. Fewer neuropathologic lesions of AD resulted in clinical signs of dementia in those with infarcts than those without. For 100% clinical expression of dementia, those with infarcts needed a mean of 1.9 or more neurofibrillary tangles in the neurocortex versus a mean of 15.7 in those without infarcts. Those findings suggest that cerebrovascular disease plays an important role in determining the presentation and severity of clinical symptoms of AD.

What Do Epidemiology Studies Show with Respect to “Vascular” Risk Factors and AD?

The Rotterdam study, a longitudinal study of over 7,000 elderly subjects, confirmed the following risk factors for AD (all of which are vascular related or reduce cerebral perfusion):

- Thrombotic Episodes
- Atherosclerosis
- Atrial fibrillation
- Hypertension
- Smoking
- Diabetes
- Hyperhomocysteinemia

Neuroimaging studies show that silent brain infarcts more than doubled (Odds Ratio 2.26) the risk of AD. Brain infarcts are common in the elderly (31%) in the Cardiovascular Health study, and are often clinically silent (89% of infarcts).

Other studies have reported stroke, coronary heart disease,
migraine, peripheral vascular disease, TIA, hyperlipidemia, high intake of saturated fat, carotid stenosis and coronary bypass surgery. Particularly important is the association of mid-life hypertension in the development of later life AD (FINMONICA\textsuperscript{13} and Honolulu-Asia Aging Study\textsuperscript{14}). Most of these risk factors for AD are also clearly risk factors for VAD.

In summary, there is considerable epidemiologic evidence supporting the concept that AD is a multifactorial disorder with a definite vascular contribution. In terms of diagnosis, therefore, the presence of vascular risk factors (VRFs) does not make a diagnosis of VAD or mixed AD with CVD. The diagnosis requires neuroimaging to confirm vascular brain damage. VRFs increase the likelihood of cognitive impairment (CI).

How do Vascular and AD Pathologies Fit into the Diagnostic Spectrum?
Two Canadian studies have suggested that approximately 75% to 80% of dementias are due to AD, VAD and mixed AD with CVD.

The spectrum of AD, VAD and mixed AD with CVD represents approximately 80% of all dementias. Many experts feel that mixed AD with CVD is the commonest dementia in those aged over 80 years. There are common risk factors and neuropathologies, and there is a critical and synergistic interplay between cerebrovascular and neurodegenerative mechanisms. The approach by the primary care physician (PCP) to treatment is simplified in that all three diagnoses share a common goal: treatment of VRFs, a treatment trial with cholinesterase inhibitors, and caregiver education and support. The progression in severity does differ with AD the worst and most predictable, with VAD often not progressing very much over several years and with mixed AD and VAD intermediate. Clinically, it is important that the PCP recognize the other common dementias: Lewy body and fronto-temporal, as the approach to care of these two dementias is different.

So What Should the PCP Do Differently?
Most PCPs would not screen a 75-year-old patient with hypertension and heart disease for cognitive impairment even though the risk for CI is over 30% (see Table 4). The elderly patient with 2 or more VRFs should be screened for cognitive impairment (either mild cognitive impairment [MCI] or early dementia). The advantages of early diagnosis of MCI is close follow-up to detect early the progression to dementia and early
treatment of VRFs which may slow progression. The advantages of early detection of dementias are shown in Table 3.

The DECIDE Study (Detection of Cognitive Impairment and Dementia in Elderly with VRFs)\textsuperscript{17} screened 1,523 patients of 122 PCPs in Canada. The eligibility criteria were age 65 years and over (mean age was 80 years), having 2 or more VRFs and the PCPs had to feel clinically there was no evidence of cognitive impairment. The screening test was animal fluency (AF) (\textit{i.e.}, name as many four-legged animals as you can think of in 1 minute). The MOCA (Montreal Cognitive Assessment)\textsuperscript{18} was the multidimensional test against which the effectiveness of AF was measured. The MOCA was chosen because it is effective in the detection of early cognitive impairment and in testing executive function, which is more likely to be impaired early when there is an element of vascular disease. The AF test was positive in 52\%, (cut off < 15); the MOCA was positive in 56\% (cut off < 26). Lessons learned were that cognitive impairment often “flies under the radar” in a PCP practice and that the 1 minute AF test may assist in screening for cognitive impairment in a higher risk population (> 2 VRFs).

**How Can a PCP Estimate the Risk of CI?**

The “rule of 2” can be used to estimate risk of cognitive impairment in elderly patients:
- The risk is 2\% at age 65 years
- Every 5 years the risk doubles
- Every vascular risk factor approximately doubles the risk
- Every 1st degree relative with dementia doubles the risk

If the risk for CI is over 20\% (therefore a high-risk subpopulation), there is reason to consider screening for CI. The American Academy of Neurology\textsuperscript{19} recommended: “general cognitive screening instruments should be considered for the detection of dementia when used in patient populations with an elevated prevalence of cognitive impairment due to age or presence of memory dysfunction.”

**How Can a PCP Quickly Screen for CI in a Busy Office?**

These 3 items (see Table 5) were chosen because the odds ratios (risk if screen positive vs. screen negative) are high especially with AF and clock drawing, and because multiple cognitive domains are assessed: memory and visual spatial problems more typical of AD and executive function more typical of AD. If one or more of the screening tests are positive, the person and an “informant” should be asked if there have been any memory or functional changes over the last 6 to 12 months, and formal cognitive tests should be done (MMSE, MOCA, etc.).
What is the Evidence that Treatment of VRFs Benefit Dementia?

Different epidemiology studies have shown variable increased risks for dementia ranging as high as 3 to 5 times in patients who have had cardiovascular events (CVA, MI, etc.)\textsuperscript{20} and 2 to 3 times for hypertension, diabetes and hyperlipidemia (from the Canadian Study on Health and Aging).\textsuperscript{21}

But does treatment of VRFs prevent/delay dementia or slow its progression? First of all, “the time” for treatment of VRFs should start in mid-life, not after 65 years when significant vascular and/or neurodegenerative pathology may already be well established. Mid-life hypertension is associated on autopsy studies in the elderly showing increased risk of plaques and tangles and of clinical AD.\textsuperscript{14} The odds ratio for dementia related to mid-life hypertension for systolic hypertension/diastolic hypertension are 3.1/1.7 (FINMONICA\textsuperscript{13}) and 4.8/4.3 (Honolulu Aging Study\textsuperscript{14}).

In general, epidemiologic studies have shown that a mid-life rise in hypertension and diabetes is associated with a rise in dementia 10 to 20 years later. To most effectively delay or prevent dementia, optimal treatment of VRFs should start in mid-life. The baby boomers are aware of the increasing risk of dementia in later life because their parents may be affected and may be more compliant with pharmacotherapy if the potential benefits with respect to dementia are discussed.

The best evidence for delay/prevention of dementia is the Syst-Eur Study\textsuperscript{22} in which those elderly treated for hypertension with a calcium channel blocker had 55% less dementia \((p < 0.05)\) over 3.9 year follow-up. There was less VAD and less AD.

For the other VRFs, there is clear evidence for CVA prevention but as of yet no clear evidence for dementia prevention in recent trials, although as stated earlier, it may be too late to treat VRF in patients over 70 years. However, based on the epidemiologic studies, especially the Nun Study, it takes only a small leap of faith to think that CVA prevention could mean dementia delay. A 5 year delay in the age of onset of dementia would reduce dementia prevalence by 50% with great individual health and socio-economic benefits.

<table>
<thead>
<tr>
<th>Benefits of “Early” Diagnosis/Treatment of Dementia</th>
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<tbody>
<tr>
<td><strong>Social</strong></td>
</tr>
<tr>
<td>Early caregiver education</td>
</tr>
<tr>
<td>Safety: compliance, driving, cooking</td>
</tr>
<tr>
<td>Advance directives planning / POA</td>
</tr>
<tr>
<td>Social/financial planning</td>
</tr>
<tr>
<td>Caregiver support and services</td>
</tr>
<tr>
<td><strong>Medical</strong></td>
</tr>
<tr>
<td>R/O Reversible causes/components</td>
</tr>
<tr>
<td>Risk factor treatment</td>
</tr>
<tr>
<td>Treatment of other diseases</td>
</tr>
<tr>
<td>AChEI treatment trial</td>
</tr>
<tr>
<td>Compliance strategies</td>
</tr>
</tbody>
</table>

What’s the Bottom Line?

- Vascular and neurodegenerative pathologies are interrelated and contribute to 80% of all dementias, that is, VAD, mixed AD with CVD, and AD. The brain as a cognitive organ is an important ‘target end organ’ for VRF treatment.
- VRFs in mid-life and late life increase the risk for dementias.
- The three greatest risk factors for...
The elderly at high risk for CI (especially related to two or more VRFs) should have cognitive screening (see Table 5).

All those with CI (MCI and dementia) should have screening and treatment for VRFs.

The treatment of VRFs has proven efficacy in CVA prevention and possible benefits for dementia delay.

Ideally treatment of VRFs should start mid-life or earlier. Treatment of VRFs in late life will prevent CVA and possibly dementia.

Useful websites:
- www.cvtoolbox.com
- www.chs.md/-index2.html
- www.diabetes.ca/cpg2000
- www.cmaj.ca/cgi

References:
1. Roth MJ. Mental Sci 1955;101:281-301.
23. Canadian Consensus Guidelines. (To be published in July 2007 CMAJ.)

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### Table 4

#### Dementia Risk Calculator

<table>
<thead>
<tr>
<th>Family history (risk doubles for each first degree relative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Mother</td>
</tr>
<tr>
<td>□ Father</td>
</tr>
<tr>
<td>□ Brother</td>
</tr>
<tr>
<td>□ Sister</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular risk factors (risk doubles for each vascular risk factor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Atrial Fibrillation</td>
</tr>
<tr>
<td>□ Diabetes</td>
</tr>
<tr>
<td>□ Heart disease (MI/CAD)</td>
</tr>
<tr>
<td>□ Hyperlipidemia</td>
</tr>
<tr>
<td>□ Hypertension</td>
</tr>
<tr>
<td>□ Smoking</td>
</tr>
<tr>
<td>□ Stroke</td>
</tr>
<tr>
<td>□ Obesity</td>
</tr>
</tbody>
</table>

Overall Risk = _______%

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### Table 5

#### Dementia Quick Screen*

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Domain Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-item recall (0-1 correct: OR 3.1; 2/3 is normal)</td>
<td>Registration, short term memory</td>
</tr>
<tr>
<td>4-legged animals in 1 minute (&lt;15: OR 20.2)</td>
<td>Executive function</td>
</tr>
<tr>
<td>Clock drawing (abnormal: OR 24)</td>
<td>Visuospatial, memory and executive function (hands at 10 past 11)</td>
</tr>
</tbody>
</table>

*Takes only 2 minutes and can be done by a physician or other care provider