VASCULAR COGNITIVE IMPAIRMENT/DEMENTIA
SETTING THE STAGE

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Issues in the Diagnosis of Vascular Cognitive Impairment and Dementia

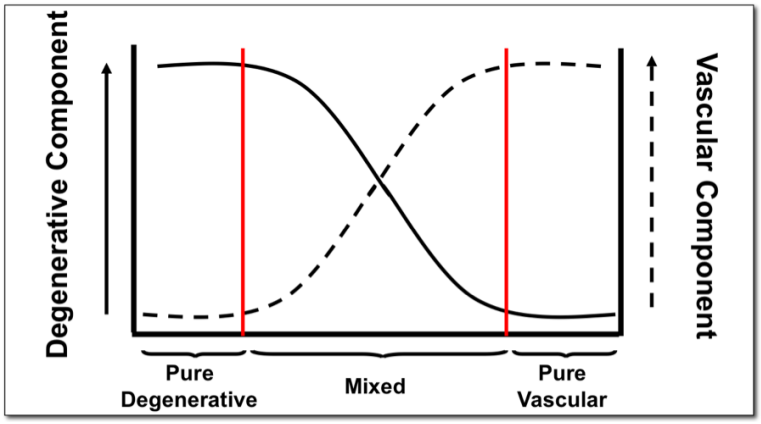
The entire field of vascular cognitive impairment (VCI) and vascular dementia (VaD) research has been limited by the imprecise use of definitions and limitations in clinical diagnosis [1]. Operationally, **cognitive impairment** refers to the presence of cognitive deficits that do not affect daily functioning; **dementia** refers to cognitive impairments that interfere with daily functioning leading to a loss of independence [2, 3]. Including the term **vascular** implies a pathophysiological cause of a patient's cognitive deficits. DSM-V removes the term "dementia" due to its negative connotation. [4] VaD is replaced by the term "Major Neurocognitive Disorder" and VCI by the term "Minor Neurocognitive Disorder."

Table 1. DSM-V Criteria for Major Neurocognitive Disorder.
One or more acquired significant impairments (independence lost) in cognitive domains. Examples:

- Memory (amnesia)
- Language (aphasia)
- Execution of purposeful movement (apraxia)
- Recognition/familiarity (agnosia)
- Visuospatial function
- Self control/management (executive function)
- Other
  - Mathematics (dyscalculia)
  - Emotional comprehension/expression (dysprosody)
  - Writing (agraphia)

For simplicity, the terms VCI and VaD are used in this syllabus.

Fig. 1. Patients Can Have Pathological Evidence of Both Vascular Injury and a Neurodegenerative Disorder



Pathological studies show varying degrees of AD, Lewy Body Dementia, and small-vessel-type changes in cognitively normal adults. [5] This raises several fundamental issues important for clinicians as they think about patients with cognitive deficits that could be related to cerebrovascular disease. As shown in Fig. 1, pathological evidence of a neurodegenerative condition often coexists in patients who also have cerebrovascular disease (modified from [2]). In some patients, one or the other of the pathologies may predominate, but each can contribute to an individual's cognitive deficits.

Further, a variety of types and extents of vascular lesions can contribute to cognitive deficits. Diifferent cognitive profiles are associated with anterior and posterior white matter MRI hyperintensity progression, even among

normal elders. [6] On a purely anatomical basis, the nature and severity of vascular-related cognitive deficits differ between patients with single as compared to multiple cortical infarcts. Strategically placed infarcts, however, can also lead to cognitive deficits. These may involve caudate, thalamus, hippocampus, and peri-Sylvian regions. There can be more diffuse ischemic injury that can be multifocal in a so-called "microvascular" distribution that involves the periventricular or subcortical white matter. Hypoperfusion may lead to "watershed" ischemic injury in both the deep hemispheric white matter or in the cortex. In addition to ischemic injury, brain hemorrhage involving cortical as well as subcortical structures can result in cognitive deficits. Therefore, although radiographic studies may provide evidence of a variety of types of vascular injury, such changes in a patient with a cognitive impairment or dementia do not mean that the radiographic lesions are their cause (or sole cause). Radiographic evidence of vascular injury does not exclude the presence of a concomitant neurodegenerative condition, and the correlation between the extent of radiographic findings and the presence or severity of a patient's cognitive deficits can be poor. The Baltimore Longitudinal Study of Aging in which all subjects had longitudinal and cognitive evaluations and postmortem neuropathological assessments found that AD accounted for 50% of the dementia with hemispheric infarcts that occurred in conjunction with AD pathology in 35% [7].

From a clinical standpoint, VCI/VaD may be diagnosed in a previously cognitively normal patient who abruptly develops cognitive deficits coincident with a new stroke (i.e., an appropriate clinical setting). VCI would be diagnosed if the cognitive deficits did not affect daily functioning with VaD diagnosed if daily functioning was impaired. Both ICD-10 and the previous DSM-IV definitions of VaD (and the DSM-V diagnosis of Vascular Major Neurocognitive Disorder, Table 1) require clinical evidence of stroke based on neurological examination findings and/or neuroimaging [3]. The definitions do, however, also differ. ICD-10 requires a temporal link between the stroke and the onset of the cognitive impairment; a temporal link is not required as part of the DSM-IV/V definition. [8]

Table 2 provides general clinical criteria for distinguishing Alzheimer's-type dementia from VaD (modified from Aggarwal and DeCarli [9].

Table 2. Clinical Features of Alzheimer's and Vascular Dementia

Feature	Alzheimer's Dementia	Vascular Dementia
Onset	Gradual	Sudden or gradual
Progression	Constant insidious	Slow, stepwise
Focal signs	Usually absent	Present
Memory	Early and severe	Mildly affected
Executive function	Late	Early and severe
Neuroimaging	Normal, atrophy	Parenchymal vascular injury

Several different schemes have been developed and used in research studies of VaD. The Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) criteria provide definitions for *Probable* VaD (dementia and at least 2 stroke by history with neurological findings with or without neuroimaging or 1 stroke with a temporal relationship with the onset of dementia, or 1 stroke outside the cerebellum by CT or MRI) and for *Possible* VaD (dementia and 1 stroke without clear relationship to the onset of the dementia and/or white matter changes on neuroimaging in a patient with vascular risk factors and the early onset of a gait disturbance or urinary incontinence) [10]. The NINDS-AIREN scheme describes *Probable* VaD (requires dementia and stroke with an abrupt onset of dementia within 3 months and a fluctuating or stepwise course) and *Possible* VaD (requires only dementia with focal neurological signs when neuroimaging is unavailable, there is no clear temporal relationship with stroke, and/or the onset of the cognitive deficit is not abrupt and the course variable) [11].

There are significant issues related to the reliability (Table 3 [12]) and validity (Table 4 [13]) of these various diagnostic criteria.

Table 3. Diagnostic Reliability

Criteria	Kappa
DSM-IV	0.59
NINDS-AIREN	
Probable	0.44
Possible	0.15
ADDTC	
Probable	0.42
Possible	0.42

Table 4. Validity (vs. Neuropathology)

	VaD (No AD Changes)		Pure AD (no Vascular Component)	
Criteria	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
NINDS-AIREN	0.58	0.80	0.43	0.91
ADDTC	0.63	0.64	0.58	0.88

Although agreed upon diagnostic criteria are lacking, the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network convened a group to identify a common set of data to be collected in studies of VCI/VaD. [14] These "harmonization standards" included suggested cognitive evaluations and schemes for neuroimaging interpretation.

As a result of varying diagnostic criteria and other methodological issues, estimates of the prevalence of these conditions based on epidemiological studies are at best uncertain [3, 9]. Given these limitations, it is estimated that the prevalence of VaD doubles every 5-10 years after age 65 affecting 1-4% of that population. It is considered the second most common cause of dementia in Western populations and surpasses AD in those over age 85 years. Dementia occurs in about 20-30% of stroke patients within 3 months with an additional 25% developing dementia over the ensuing 3 years. Half of those with VCI progress to dementia over 5 years.

Risk Factors and Management

A genome-wide association study of data from METASTROKE 1 (15,916 IS cases and 68,826 controls) and the International Genomics of Alzheimer's Project (IGAP; 17,008 AD cases and 37,154 controls) found a shared genetic susceptibility to AD and small vessel stroke. [15] Another whole genome association showed significance for rs12007229, located on the X chromosome near the androgen receptor gene. [16] The association was confirmed in 2 independent populations. The clinical significance of the finding needs to be established and the association further confirmed in additional cohorts.

As shown in Fig. 2, the there is potential overlap in the pathophysiologies of vascular disease and AD [3]; This has also been described as the "two hit theory." [17] Not only may VCI/VaD occur in patients with other neurodegenerative conditions, but as shown in Table 5, there is an overlap between risk factors for the two conditions [3]. Further, vascular risk factors can promote the progression from mild cognitive impairment to Alzheimer's Disease. [18]

Fig. 2. Overlap in Pathophysiologies of Vascular Injury and AD.

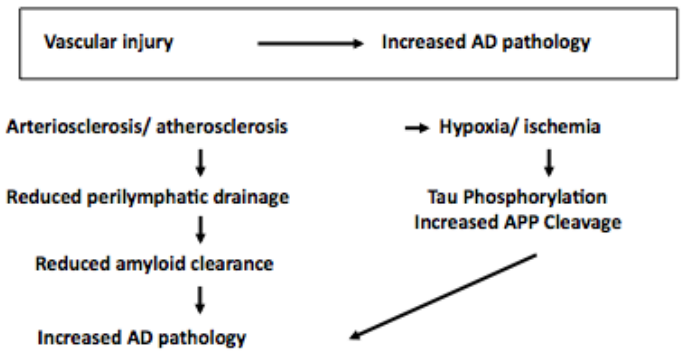


Table 5. Risk Factors for VaD and AD

Factor	Vascular Ds.	AD
Advancing age	+	+
Hypertension	+	+
Smoking	+	+
CHD	+	+
Diabetes	+	+
apoE4	+	+
Dyslipidemia	+	+/-
Inc. Homocysteine	+	+/-
Obesity	+	+/-

(APP, Amyloid Precursor Protein)

Given these overlaps, measures aimed at modifying vascular risk factors might be expected to reduce the incidence of dementia, regardless of whether it is on the basis of vascular disease or AD. At least one observational study found that treatment of vascular risk factors in patients with AD, but no vascular disease was associated with slower cognitive decline [19]. Data from the Framingham Heart Study suggest that the incidence of dementia declined by 44% in the study's 4th epoch (2004-2008) compared to the first epoch (1977-1983) with a 20% decline in the incidence of dementia per decade (HR 0.80, 95% CI 0.72-0.90). [20] Although the decline in Alzheimer's disease was not significant (p for trend=0.052), there was a decline in VaD (p for trend=0.004). The estimates were unchanged after adjustment for preexisting or incident stroke, although the risk of dementia after stroke declined over time. Adjustment for the Framingham Stroke Risk Profile Score or its components at baseline or midlife did not fully explain the lowered risk of VaD. Changes in risk factors not assessed in the Framingham Study such as diet and exercise or other unmeasured factors might have contributed to the decline.

Summary

A variety of factors hamper the clinical diagnosis of VCI/VaD that carry over to epidemiological and observational studies as well as clinical trials. There is an overlap between VCI/VaD and dementias related to neurodegenerative conditions. Because of shared risk factors, including genetic susceptibility, treatments aimed at reducing the incidence and progression of cerebrovascular disease may also reduce the development or progression of cognitive impairment and dementia.

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