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The Clinical Diagnosis of Vascular Dementia: A Comparison Among Four Classification Systems and a Proposal for a new Paradigm*

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ABSTRACT

Throughout the 1990s a variety of schemes for the diagnosis of Vascular Dementia (VaD) were proposed, including the ADDTC criteria for Ischemic Vascular Dementia, the NINDS-AIREN criteria for Vascular Dementia, Bennett's criteria for Binswanger's disease, and the ICD-10 criteria for Vascular Dementia. We undertook a retrospective analysis of a series of ambulatory outpatients with dementia to determine the prevalence with which patients were diagnosed by each of these diagnostic schemes, and to survey the clinical characteristics associated with VaD. We found that the diagnostic schemes for VaD were not interchangeable; patients diagnosed with VaD using one set of criteria were not necessarily diagnosed with VaD using other criteria. The most common clinical characteristics associated with VaD, regardless of the diagnostic scheme that was used, were hypertension, extensive periventricular and deep white matter alterations on MRI (leukoaraiosis), and differential impairment on neuropsychological tests that assess the ability to establish/maintain mental set and visuoconstruction, with relatively higher scores on tests of delayed recognition memory. Interestingly, the majority of VaD patients obtained low scores on the Modified Ischemic Scale, since cortical infarcts and a history of a sudden onset and/or step-wise decline in cognitive function were rare. We conclude that the current diagnostic schemes for VaD do not necessarily consider the heterogeneous nature of VaD. A new paradigm that seeks to *describe*, in addition to diagnosing dementia associated with cerebrovascular disease is discussed.

INTRODUCTION

Since the introduction of MRI technology, there has been a renewed interest in the phenomenon of Vascular Dementia (VaD). During the 1990s, a variety of new diagnostic criteria were proposed including Bennett's criteria for Binswanger's Disease (BD; Bennett, Wilson, Gilley, & Fox,

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1990) the ICD-10 criteria for Vascular Dementia (World Health Organization; WHO, 1993), the Alzheimer's Disease Diagnostic and Treatment Center's (ADDTC) criteria for Ischemic Vascular Dementia (IVD; Chui et al., 1992), and the National Institute of Neurological Disorders and Stroke with the Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria for Vascular Dementia (NINDS-AIREN; Roman et al., 1993).

While the reliability of the clinical diagnosis of Alzheimer's disease (AD) partially derives from the predictable nature and location of its neuropathology (Arnold, Hyman, Damasio, & Van Hoesen, 1991), such is not the case with respect to VaD. By contrast, the characteristics that underlie the clinical diagnosis of VaD can be quite heterogeneous as reflected in the discrepancy among the clinical criteria emphasized by the various diagnostic schemes listed above. Such clinical heterogeneity suggests the existence of several related, but separate disease pathways involved in VaD (Bowler & Hachinski, 1997). A comparison of these schemes illustrates the varying diagnostic importance placed on the presence of such clinical characteristics as a history of vascular risk factors, evidence of a step-wise cognitive decline, neuroimaging evidence of vascular changes, and a temporal relationship between a vascular event and the onset of cognitive decline.

For example, Bennett's criteria (Bennett et al., 1990) for the diagnosis of Binswanger's disease (BD) places particular emphasis on neuroradiological evidence of visibly significant, bilateral leukoaraiosis without substantial cortical lesions contributing to the dementia. Furthermore, there must be clinical evidence of vascular risk factors such as hypertension, focal neurologic disease and/or evidence of subcortical cerebral dysfunctions such as gait disturbance or urinary incontinence. While these criteria show a high degree of specificity for BD (only 1.6% of AD patients met these criteria), previous research has found that this diagnostic scheme was unable to distinguish between BD and mixed dementing illnesses (Bennett et al., 1990), suggesting that this set of diagnostic criteria is not exclusive to a pure form of BD.

Alternatively, the ICD-10 criteria require a different set of clinical characteristics to diagnose VaD including an unequal distribution of higher cognitive functions and a history of significant cerebrovascular disease reasonably related to the dementia (WHO, 1993). Unfortunately, concrete operational definitions of these concepts are not provided, and neuroimaging data that may provide crucial evidence of vascular pathology are not integrated into the diagnostic formula. Thus, Wetterling, Kanitz, and Borgis (1994) were able to show that only 25% of a group of 72 demented patients with evidence of vascular lesions on CT met the ICD-10 criteria for VaD. Furthermore, despite the added sophistication of VaD subtypes outlined by the ICD-10 (acute onset, multi-infarct, subcortical, and mixed VaD), Wetterling et al. (1994) could diagnose only 61% of their patients into any one of these subtypes.

A third diagnostic scheme, the ADDTC criteria for Ischemic Vascular Dementia (IVD, Chui et al., 1992), was purposely constructed to resemble the structure of the NINCDS-ADRDA criteria for AD. The ADDTC classification scheme attempts to differentiate between definite, probable, possible, and mixed IVD. In order to meet criteria for probable IVD, there must be evidence of two or more ischemic strokes on the basis of imaging data, history or examination; or the occurrence of a single stroke that is temporally related to the onset of dementia. In addition, evidence of at least one infarct outside the cerebellum by CT or T1-weighted MRI is required. The ADDTC criteria for possible IVD are very similar to Bennett's criteria for Binswanger's disease (Bennett et al., 1990). While a strength of the ADDTC criteria is the incorporation of neuroimaging data, these criteria have been criticized for possibly over-diagnosing IVD since it is unclear whether the mere presence of two or more infarcts from imaging studies is too liberal a link between neuroimaging findings and cognitive deficits (Loeb & Meyer, 2000).

Finally, the NINDS-AIREN criteria (Roman et al., 1993) also attempt to differentiate definite, probable, and possible VaD. A diagnosis of probable VaD places particular emphasis on a decline in memory, and a temporal relationship between the onset of the dementia and a known

cerebrovascular event. However, since this diagnostic scheme was proposed, a growing literature has emerged to suggest that many patients with VaD display greater impairment on tests of executive functions than on tests of memory (Libon et al., 1997, 2001; Looi & Sachdev, 1999). Furthermore, when vascular neuropathology is confined to subcortical regions of the brain, the onset and course of the resultant dementing illness is often insidious and progressive. Thus, it is difficult, if not impossible, to determine a temporal relationship between a discrete cerebrovascular event and cognitive decline (Loeb & Meyer, 2000). It is possible that the diagnostic schemes discussed above differ substantially in their characterization of VaD because they very likely identify separate vascular disease pathways. This may be reflected in the variation that exists between the diagnostic sensitivity and specificity of these schemes. For example, Gold et al. (1997) analyzed autopsy evidence from 40 patients with VaD, 32 patients with AD, and 41 patients with mixed dementia (MD) to assess the sensitivity and specificity of the ADDTC and NINDS-AIREN diagnostic criteria. While both diagnostic schemes excluded the majority of AD patients from a VaD diagnosis (ADDTC – 87%; NINDS-AIREN – 91%), the ADDTC criteria diagnosed far more mixed dementia patients with VaD than did the NINDS-AIREN criteria. However, the NINDS-AIREN failed to diagnose 9 patients with a clear history of stroke due to an absence of focal neurologic signs on physical examination. Specifically, the ADDTC criteria yielded sensitivity and specificity rates of 63 and 64%, respectively while the NINDS-AIREN criteria rates were 58 and 80%, respectively.

Additional studies underscore the significant discrepancies with respect to diagnostic sensitivity and specificity (Gold et al., 2002; Pohjasvaara, Mantyla, Ylikoski, Kaste, & Erkinjuntti, 2000). For example, when Chui et al. (2000) asked a panel of clinicians to diagnose a sample of 25 cognitive impairment case vignettes, 6% of the cases were diagnosed with probable VaD according to NINDS-AIREN criteria, while 20.6% met criteria for ADDTC probable. Finally, Wetterling, Kanitz, and Borgis (1996) found that while 84.6% of a group of dementia patients was diagnosed with VaD by at least 1 of 4 diagnostic schemes, only 8.5% met criteria for more than one diagnostic scheme (ADDTC, ICD-10, DSM IV, & NINDS-AIREN). Moreover, these diagnostic schemes varied with respect to their sensitivity, with 38.9% of patients diagnosed by the ADDTC, 35.6% by the ICD-10, and only 20.3% by the NINDS-AIREN criteria.

The need for an accurate characterization of VaD is underscored by findings suggesting that the incidence of VaD has been reported to exceed that of AD in some parts of the world including Asia (Li et al., 1989; Suzuki, Kutsuzawa, Nakajinia, & Hatano, 1991; Yamaguchi, Ogata, & Yoshida, 1991), Italy (Rocca et al., 1991) and Sweden (Skoog, Nilsson, Palmertz, Andreasson, & Svanborg, 1993). Moreover, the ability to accurately diagnose VaD is essential in order to plan for the appropriate clinical management of patients, and to dissociate VaD from other types of dementia in conducting clinical trials. Unfortunately, epidemiological studies of the incidence of VaD remain questionable so long as the diagnostic criteria remain inconsistent and uncertain.

Purpose of Present Investigation

In the present study we conducted a retrospective review of the clinical characteristics of patients whose dementia was assessed at a suburban, university affiliated, outpatient memory clinic. The purpose of the present study has three main objectives. First, we sought, within each scheme, to conduct a survey of the prevalence with which patients met the varying criteria for VaD according to the diagnostic schemes discussed above. Second, we sought to conduct a survey of the various clinical characteristics within each scheme that most frequently underlie the diagnosis of vascular dementia. Lastly, we assessed the nature and prevalence of additional clinical characteristics such as vascular risk factors, the Modified Ischemic Scale score (Rosen, Terry, Fuld, Katzman, & Peck, 1980), the severity of MRI periventricular and deep white matter alterations or leukoaraiosis (Junque et al., 1990), and performance on neuropsychological measures as potential aids in characterizing VaD.

METHODS

Participants

The participants in this study were evaluated at the Crozer Chester Medical Center's Alexander Silberman Geriatric Assessment Program Center. An interdisciplinary team including a social worker, geriatrician, neurologist, psychiatrist, and neuropsychologist examined each patient. Neuroimaging (MRI/CT), laboratory studies including ECG studies, neuropsychological assessments, and structured clinical interviews were obtained for all patients. All data were obtained over a 3-day period. Based on this information, a clinical diagnosis of dementia was determined. On the basis of the team diagnosis 46 patients were diagnosed with probable dementia of the Alzheimer's type according to NINCDS-ADRDA criteria (McKhann et al., 1984), and 37 patients were diagnosed with vascular dementia. No between-group differences were found with respect to age, $t[81] = 0.64$, *ns*, education, $t[81] = 1.16$, *ns* level of dementia as assessed with the Mini-Mental Status Examination, (Folstein, Folstein, & McHugh, 1975; $t[81] = 0.424$, *ns*), or level of depression as assessed with the Geriatric Depression Scale, Yesavage et al., 1986; $t[81] = 0.73$, *ns*; Table 1).

At the time this research was initiated patients with suspected vascular dementia were diagnosed using Bennett's criteria for Binswanger's disease, and the ADDTC criteria for possible and probable Ischemic Vascular Dementia. When the NINDS-AIREN and ICD-10 diagnostic criteria were proposed, clinical data for all patients was reviewed, and patients meeting these diagnostic criteria were noted. After 1994, patients with suspected vascular dementia were routinely classified using all four diagnostic schemes. All patients diagnosed with dementia presented with a decline in ADL and/or IADL functions as documented by information provided by patients' families. In addition, all patients diagnosed with dementia obtained a CDR score of 1 or greater. Patients were excluded if there was any history of head injury, substance abuse, major psychiatric disorders (including major depression), epilepsy, B12, folate, or thyroid deficiency. This information was gathered from a knowledgeable family member and medical records.

Procedure

Medical histories, clinical interviews, neurologic/psychiatric examination results, and neuroradiological findings were reviewed in order to classify each patient according to the following criteria: NINDS-AIREN criteria for probable/possible VaD (Roman et al., 1993); ICD-10 criteria for VaD (WHO, 1993), ADDTC criteria for probable/possible IVD (Chui et al., 1992), and Bennett's criteria for BD (Bennett et al., 1990). The following data were examined for each patient: MRI findings, the Modified Ischemic Scale (MIS; Rosen et al., 1980), the leukoaraiosis score of Junque (Junque et al., 1990), the presence of cardiovascular risk factors such as hypertension, diabetes, and heart disease, and performance on neuropsychological measures.

Magnetic Resonance Imaging

All MRIs were conducted on a Siemens 1.5 Tesla machine. Both T1 (TR-500 ms, TE-15 ms) and T2

Table 1. Demographic Data (Mean & Standard Deviation).

	AD	VaD
Age	77.83 (5.38)	78.70 (7.05)
Education	11.96 (2.66)	11.27 (2.70)
MMSE	21.33 (3.71)	20.95 (4.47)
GDS	5.43 (4.12)	7.32 (4.76)
Neuropsychological variables (mean & standard deviations)		
Mental Control AcI	70.66 (15.76)	47.06 (23.77)
Letter fluency ('FAS')	22.49 (9.42)	16.14 (7.56)
Boston Naming Test	32.91 (12.05)	35.82 (10.71)
'animal' fluency – total responses	6.89 (2.67)	7.71 (3.14)
'animal' fluency – AI	2.68 (.91)	3.32 (.68)
Clock drawing errors	3.35 (1.79)	5.86 (2.58)
CVLT-9 recognition		
Discriminability index	64.25 (12.81)	79.85 (11.01)

Note. AD: Alzheimer's disease; VaD: Vascular Dementia; MMSE: Mini Mental State Examination; GDS: Geriatric Depression Scale; AcI: Mental Control Accuracy Index; AI: 'animal' fluency Association Index; CVLT: California Verbal Learning Test.

weighted (TR-4000 ms, TE-90 ms) studies were obtained for each patient. The severity of white matter alterations was quantified using the 40-point leukoaraiosis scale (LA) described by Junque et al. (1990). Leukoaraiosis is a generic term, originally proposed by Hachinski and colleagues (1987), to describe white matter alterations on CT/MRI scans. The term leukoaraiosis was not intended to be associated with any clinical or diagnostic phenomenon. Leukoaraiosis generally refers to either periventricular white matter changes which are visible along the borders of the lateral ventricles, or deep white matter changes which occur in areas of the brain adjacent to the lateral ventricles.

We measured MRI white matter alterations using the leuokoaraiosis scale of Junque (Junque et al., 1990). This is a semi-quantitative scale. Each hemisphere is divided into five areas: the frontal centrum semiovale, the parietal centrum semiovale, the white matter around the frontal horns, the white matter around the body of the lateral ventricles, and the white matter around the atrium and occipital horns. The severity of white matter alterations in each area is graded from 0 to 4 and scores are summed across all 10 areas for a possible total of 40 points. As noted above, some of the diagnostic schemes under consideration require evidence of significant subcortical white matter alterations. In the present study we used a LA score of 10 or greater to operationally identify instances when subcortical white matter disease may be clinically important. Our rationale for using this score was two-fold. First, a score of 10 represented the median value regarding the distribution of LA scores within our sample. Second, Roman et al. (1993) have suggested that in order for periventricular and deep white matter alterations to be considered clinically significant, one-fourth, or 25% of the total white matter should be involved. A LA score of 10 fulfills this criterion. All LA scores were calculated by board certified neuroradiologists who were blind to relevant clinical information regarding these patients. Information regarding the presence of cortical and subcortical infarcts was also provided.

Neuropsychological Assessment

Listed below are the neuropsychological measures, as well as the dependent variables, derived from each test. Means and standard deviations for each variable are listed in Table 1.

Capacity to Establish/Maintain Mental Set

Recent research has shown that patients with VaD and dementia associated with Parkinson's disease (PD) present with differential impairment regarding their ability to establish and maintain a mental set (Lamar et al., 2002). In the current research this domain of cognitive functioning was assessed with the Boston Revision of the Wechsler Memory Scale – Mental Control (WMS-MC) subtest (Cloud et al., 1994; Lamar et al., 2002). The dependent variable for this test was an Accuracy Index (AcI) derived from the three non-automatized tasks (i.e., reciting months backwards, alphabet rhyming, & alphabet visualization). Patients were allowed to work as long as necessary on these tasks provided they were working meaningfully. The dependent variable derived from this test was the WMS-MC Non-automatized Accuracy Index (AcI). This index was based on the following algorithm: $\text{AcI} = [1 - (\text{false positive} + \text{misses/\# possible correct})] * 100$, and yields a percentage score ranging from 0 to 100, such that patients obtaining a score of 100% correctly identified all targets and made no false positive responses or misses. A composite score assessing performance on the three non-automatized mental control tasks was calculated by averaging the AcI for all tasks for each patient.

Capacity to establish and maintain a mental set was also assessed with tests of letter word list generation (WLG; Spreen & Strauss, 1991). On the letter WLG test, patients were given 60 s to generate words beginning with a specified letter (i.e., 'FAS') excluding proper nouns. The dependent variable was the number of unique, non-proper noun responses summed for the letters F, A, and S. Lamar et al. (2002) have argued that performance on both tests provides a measure of working memory as described by Fuster (1997).

Lexical/Semantic Functioning

Lexical/semantic functioning was assessed with the 60-item version of the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983) and a test of category ('animal') word list generation (Carew, Lamar, Cloud, Grossman, & Libon, 1997; Monsch et al., 1992). The dependent variable for the BNT was the number of correct and semantically cued responses. On the 'animal' WLG test, patients were given 60 s to generate exemplars. The dependent variable was the total Association Index (AI), a scoring technique that measures the semantic integrity between successive responses. A high score on this measure is believed to reflect generally intact semantic memory stores. Complete details regarding the AI can be found in Carew et al. (1997), and the Appendix. Similar scoring techniques have been described by Troyer, Moscovitch, Winocur, Leach, and Freedman (1998).

Visuoconstructional Functioning

Visuoconstructional functioning was assessed by asking patients to draw the face of a clock with the hands set for 'ten after eleven' in both a command and copy condition (Goodglass & Kaplan, 1983). Following procedures described by Libon and colleagues (Libon,

Malamut, Swenson, Sand, & Cloud, 1996a), the dependent variable was the total number of errors.

Delayed Recognition Memory

Delayed recognition memory was assessed with the 9-word version of the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987; Libon et al., 1996b). For the present research, the recognition discriminability index was selected for analysis as the dependent variable on the basis of research carried out by Libon et al. (1998). In that study the recognition discriminability index, rather than other CVLT measures, such as delayed free recall, was found to correlate highly with the volume of the hippocampus and parahippocampal gyrus, structures known to be involved in the learning of new information.

Table 2. Frequency of Diagnosis for Each Diagnostic Scheme.

Diagnostic scheme	*n*	Percent
ADDTC probable IVD	28	75.6
ADDTC possible IVD	9	24.3
Binswanger's disease	18	48.6
ICD-10	9	24.6
NINDS-AIREN – possible VaD	6	16.2
NINDS – probable VaD	4	10.8
Patients diagnosed clinically with Alzheimer's disease also meeting criteria for vascular dementia		
ADDTC probable IVD	7	15.2
ADDTC possible IVD	1	2.1

RESULTS

Diagnostic Prevalence and Clinical Characteristics

When each of the diagnostic schemes was applied to the sample of patients with AD, only the ADDTC criteria resulted in a false positive diagnosis of VaD (Table 2). As indicated below, the various criteria needed to diagnose VaD differed from scheme to scheme. For example, 7 patients with AD (15.2%) also met criteria for probable IVD, and 1 patient with AD (2.1%) met criteria for possible IVD. When each of the diagnostic schemes was applied to the entire sample of patients with VaD, only 45.9% (17/37) were diagnosed by more than one scheme. Most patients met criteria for probable IVD on the basis of the ADDTC criteria (75.6% or 28/37). This was followed by Bennett's criteria for BD at 48.6% (18/37), the ADDTC criteria for possible IVD at 24.3% (9/37), the ICD-10 criteria for VaD at 24.3% (9/37), the NINDS-AIREN criteria for possible VaD at 16.2% (6/37), and the NINDS-AIREN criteria for probable VaD at 10.8% (4/37; Table 2).

We also sought to determine the prevalence with which individual clinical characteristics underlie a diagnosis of VaD on each classification scheme (Table 3). This was done only for patients diagnosed with VaD. As seen in Table 3, the individual clinical characteristics underlying a diagnosis of VaD within a given scheme tend to be fairly evenly distributed. That is, no particular clinical characteristic seems to occur more frequently in the diagnoses of VaD, except in the case of those patients diagnosed with ADDTC Probable IVD. While 100% of such patients presented with neuroradiological evidence of at least two ischemic strokes outside the cerebellum (28/28), far fewer patients presented with evidence of ischemic stroke on the basis of history (46% or 13/28) or neurologic examinations (28.5% or 8/28). Furthermore, only 1 of 28 patients had a documented stroke with a temporal relationship to the onset of the dementia. Such findings present striking evidence for the role of neuroimaging in the diagnostic process. Within the context of our sample of patients this finding challenges the usefulness of requiring evidence of a temporal relationship between a vascular event and cognitive decline in order to diagnose VaD.

Neuropsychological Functioning

Individual and composite *z*-scores were calculated for all of the mental set, visuoconstructional, lexical/semantic, and memory tests. These *z*-scores were based on the performance of normal control participants who were matched for age and education (Libon et al., 1996, 1997, 2001; Table 4). Non-demented elders ($n = 19$) were living independently in the community. There was no difference in age or education between this group and the two dementia groups. Non-demented elders were included if their scores on the Mini-Mental Status Exam (MMSE; Folstein et al., 1975), and Geriatric Depression Scale

Table 3. Frequency of Each Criterion Within Diagnostic Schemes.

	n	Percent
California criteria of Chui for probable IVD (n = 28)		
Dementia with evidence of two or more ischemic strokes on the basis of		
(1) History	13	46.4
(2) Neurological signs and/or	8	28.5
(3) Neuroimaging studies *or*	28	100.0
(4) A single stroke with clear temporal relationship to dementia onset	2	7.1
Evidence of at least one infarct outside the cerebellum on MRI	28	100.0
If item 3 is not present, then must have both 1 & 2		
California criteria of Chui for possible IVD (n = 9)		
Dementia associated with		
(1) History of a single stroke without a temporal relationship to the onset of the dementia	1	11.1
(2) Binswanger's Syndrome (without multiple strokes) that includes all of the following:	9	100.0
(a) Urinary incontinence not explained by urologic disease or	6	66.6
a gait disturbance	7	77.7
(b) Vascular risk factors	9	100.0
(c) Extensive white matter changes on imaging	9	100.0
Criteria for Binswanger's disease (Bennett et al., 1990; n = 18)		
Dementia confirmed by clinical examination including neuropsychological evaluation associated with one finding from two of the following three groups of characteristics		
(1) Presence of vascular risk factors or systemic vascular disease (e.g., HTN, DM, CHF)	17	94.4
(2) Evidence of focal cerebrovascular disease illustrated by the presence of focal neurological signs	9	50.0
(3) Evidence of subcortical dysfunction such as a Parkinsonian gait	15	83.3
(4) Logical evidence of bilateral Leukoaraiosis or bilateral and multiple/diffuse T2 MRI white matter alterations $>2 \times 2$ mm	18	100.0
ICD-10 criteria for Vascular Dementia (n = 9)		
Dementia associated with		
(1) Unequal distribution of cognitive deficits	9	100.0
(2) Evidence of focal brain damage	9	100.0
(3) Evidence of significant cerebrovascular disease judged to be related to the aetiology of the dementia	6	66.6
ICD-10 subtypes		
(1) Acute and/or MID onset: dementia develops within 1–6 months	3	33.3
(2) Subcortical Vascular Dementia	9	100.0
(a) With a history of hypertension	9	100.0
(b) Evidence of clinically relevant deep white matter alterations	9	100.0
(3) Mixed cortical/subcortical: A combination of MID and subcortical types	1	11.1
NINDS-AIREN criteria for probable Vascular Dementia (n = 4)		
Dementia in conjunction with		
(1) Focal neurological signs on neurology examination *and*	4	100.0
(2) Evidence of relevant cerebrovascular disease derived from brain imaging studies	4	100.0
(3) A relationship between 1 and 2 including one or more of the following clinical characteristics		
(a) Onset of dementia occurs within 3 months of a documented stroke *or*	2	50.0
(b) Abrupt onset of cognitive impairment *or*	2	50.0
(c) Step-wise/fluctuating deterioration of cognitive impairment	1	25.0

(*continued*)

Table 3. (*continued*).

	n	Percent
NINDS-AIREN criteria for possible Vascular Dementia (n = 6)		
Dementia in conjunction with		
(1) Presence of focal signs, but confirmatory evidence of cerebrovascular disease from imaging studies is missing *or*	0	0
(2) Presence of focal signs, but no temporal relationship to dementia onset *or*	6	100.0
(3) Patients with subtle onset or variable clinical course regarding cognitive functioning with evidence of relevant cerebrovascular disease	0	0

Table 4. Neuropsychological Test Data and Modified Ischemic Scale.

	Executive control	Visuoconstruction[a]	Language/ semantic	Declarative memory
(a) *Neuropsychological Test Data*				
Alzheimer's disease	−1.7 (.96)	1.2 (1.1)	−2.3 (1.5)	−6.5 (2.6)
Vascular Dementia	−3.1 (1.1)	2.9 (1.7)	−1.2 (.96)	−3.2 (2.2)
ADDTC probable	−3.2 (1.1)	2.9 (1.7)	−1.3 (.90)	−3.4 (2.3)
ADDTC possible	−2.4 (1.3)	2.9 (1.7)	−1.0 (1.1)	−2.6 (1.9)
Binswanger's disease	−2.9 (.87)	3.0 (1.6)	−1.2 (1.0)	−3.2 (1.9)
ICD-10	−3.1 (.93)	3.2 (1.5)	−1.7 (1.0)	−3.7 (1.7)
AIREN probable	−3.0 (.83)	3.6 (1.4)	−1.3 (.44)	−4.3 (2.3)
AIREN possible	−3.1 (.95)	2.6 (1.6)	−1.7 (1.2)	−2.8 (1.3)

	M	*SD*
(b) *Modified Ischemic Scale*		
Alzheimer's disease	0.48	0.86
Vascular Dementia	2.41	2.23
California criteria – probable IVD	2.89	2.35
California criteria – possible IVD	0.89	0.60
Binswanger's disease	2.83	2.73
ICD-10 – VaD	4.78	2.73
NINDS-AIREN – probable VaD	6.50	3.38
NINDS-AIREN – possible VaD	3.17	2.14

Note. [a]Performance on the visuoconstruction tests (clock drawing) is based on errors. Therefore, a positive *z*-score reflects greater number of errors and concomitant worse test performance.

(GDS, Yesavage, 1986) were ≥27, and 10, respectively. The CDR scores for all non-demented elders was 0.

Comparisons of all neuropsychological data were conducted using Multivariate Analysis of Variance (MANOVA) between AD patients and the entire VaD group. This MANOVA yielded a statistically significant effect for group, $F[5, 37] = 13.70$, $p < .001$. Follow-up comparisons found a significant dissociation such that patients with AD obtained relatively higher scores on tests of mental set, $F[1, 41] = 16.79$, $p < .001$, and visuoconstruction, $F[1, 41] = 16.02$, $p < .001$, than did patients with VaD. Conversely, patients with VaD obtained relatively higher test scores on tests of lexical/semantic knowledge, $F[1, 41] = 7.53$, $p < .009$, and delayed recognition memory, $F[1, 41] = 16.73$, $p < .001$, than did patients with AD. Moreover, an examination of Table 4a reveals that a double dissociation exists within these areas of neuropsychological functioning. Specifically, the scores obtained by patients with AD within the

domains of mental set and visuoconstruction were often almost *twice* as high compared to the VaD group; whereas the scores obtained by patients with VaD on tests of lexical/semantic knowledge and delayed recognition memory, were almost *twice* as high as compared to patients with AD.

Furthermore, as seen in Table 4a, this dissociation is maintained when each individual VaD diagnostic scheme was compared to the AD group. All six MANOVAs were significant at $p < .001$. Similarly, follow-up analyses continued to show that when each diagnostic scheme for VaD was compared to the AD group, patients with VaD obtained higher scores within the domains of lexical/semantic knowledge and delayed recognition memory, whereas the AD group obtained higher scores within the domains of mental set and visuoconstruction. All of these statistical comparisons were significant at $p < .01$ or higher.

Modified Ischemic Scale Scores

Modified Ischemic Scale (MIS) scores (Rosen et al., 1980) were calculated for each patient (Table 4b). According to Rosen et al. (1980), a score of 3 or less supports a diagnosis of AD, while a score of 4 or more suggests the presence of either a mixed or multi-infarct dementia. In this study, the mean and standard deviation for MIS scores for AD patients and the VaD group as a whole were significantly different (AD $M =$ 0.48[0.86]; VaD $M = 2.41$ (2.23), $t[81] = 5.38$, $p < .001$). Interestingly, however, the mean for the entire VaD group was in the range traditionally associated with AD. When each diagnostic scheme for VaD was examined, there was a great deal of variability in MIS scores. For example, patients diagnosed with NINDS-AIREN probable VaD obtained the highest MIS score ($M = 6.50$, $SD = 3.38$), followed by the ICD-10 ($M =$ 4.78, $SD = 2.73$), NINDS-AIREN possible VaD ($M = 3.17$, $SD = 2.14$), Bennett's criteria for BD ($M = 2.83$, $SD = 2.73$), ADDTC probable IVD ($M = 2.89$, $SD = 2.35$), and ADDTC possible IVD ($M = 0.89$, $SD = 0.60$). More importantly, however, the MIS scores for only 2 of the 6 diagnostic schemes under consideration were within the range for vascular dementia when conventional guidelines (Rosen et al., 1980) are used. Moreover, a comparison of mean MIS scores, and diagnostic frequency for each scheme reveals an inverse relationship such that the higher the mean MIS score, the lower the diagnostic frequency.

MRI Data and Vascular Risk Factors

Not surprisingly, patients with Alzheimer's disease presented with considerably less leukoaraiosis when compared to the entire group of patients with VaD, $t[82] = 8.70$, $p < .001$, Table 5.

Table 5. Leukoaraiosis Scale.

	M	*SD*
Alzheimer's disease	5.48	4.03
Vascular Dementia	14.94	5.68
California criteria – probable IVD	15.69	5.80
California criteria – possible IVD	13.67	4.72
Binswanger's disease	16.11	5.62
ICD-10 – VaD	18.00	6.00
NINDS-AIREN – probable VaD	22.70	4.57
NINDS-AIREN – possible VaD	13.56	3.94

Table 6. Vascular Risk Factors.

Vascular risk factors	Hypertension	Diabetes	Heart disease
Alzheimer's disease	10/46	4/46	5/46
Vascular Dementia	27/37	5/37	13/37
California criteria – probable IVD	21/28	3/28	10/28
California criteria – possible IVD	5/9	1/9	1/9
Binswanger's disease	11/18	3/18	3/18
ICD-10 – VaD	6/9	1/9	3/9
NINDS-AIREN – probable VaD	3/4	1/4	1/4
NINDS-AIREN – possible VaD	4/6	0/6	2/6

However, when all of the diagnostic schemes for VaD were compared to each other, no statistically significant differences were found among LA scores. MRI scans identified 6 cortical infarcts in the VaD as a whole. Patients with AD presented with 6 cortical, but only 4 subcortical infarcts.

With respect to vascular risk factors (Table 6) as a whole, greater numbers of patients with VaD presented with hypertension ($\chi^2 = 21.78, p < .001$) and heart disease ($\chi^2 = 7.10,\ p < .008$) as compared to the AD group. However, the relative proportion of patients with these illnesses did not differ among the various VaD diagnostic schemes. Thus, it appears that a high LA score and the presence of certain vascular risk factors are fairly consistent markers of vascular pathology regardless of the diagnostic scheme for VaD under consideration.

DISCUSSION

Review of Findings

The purpose of the current research was to assess the prevalence with which patients met various criteria for VaD according to the diagnostic schemes discussed above, and to conduct a survey of the clinical characteristics underlying the diagnosis of VaD for each diagnostic scheme. In addition, we assessed the relationship between the clinical diagnosis of VaD and other clinical characteristics such as the Modified Ischemic Scale score, leukoaraiosis as seen on MRI scans, vascular risk factors, and neuropsychological function. Consistent with past research, we found widespread differences among the diagnostic schemes for VaD such that only 45.9% of patients met criteria for more than one diagnostic scheme. It is important to note that each of the diagnostic criteria discussed above are intended to make a distinct classification. As such, this might limit sensitivity in the service of specificity.

An issue that needs to be addressed is the *typicality* of our group of patients with VaD. Or, to state the issue in another way, one might question whether our group of patients with VaD is truly *representative* of vascular dementia as a whole. In our experience the most frequent type of cerebrovascular lesion(s) among dementia outpatients involves periventricular and deep white matter alterations, rather than actual cortical or subcortical strokes. We maintain that such patients represent one of several pathways leading to vascular dementia.

The patients with vascular dementia described in this study were generally ambulatory, and relatively medically well and stable. As such, this sample may differ from other groups of VaD patients that might exist in other settings. This may have accounted for the fact that obvious or more traditional signs of cerebrovascular disease such as significant cortical stroke, a history of a step-wise cognitive decline, and documented evidence of a temporal relationship between cognitive decline and cerebrovascular disease were rare among these patients. This undoubtedly accounts for the low MIS scores among patients. Specifically, except for patients diagnosed with vascular dementia using the ICD-10 and NINDS-AIREN criteria for probable VaD, the MIS scores for all other diagnostic schemes were in the range generally associated with AD rather than VaD. We acknowledge that if our patients with VaD were drawn from a different setting such as an acute rehabilitation setting, our findings could have been very different. Indeed, these observations embody the very nexus of the controversy surrounding the clinical relevance of cerebrovascular disease when the course of the dementing illness is insidious and progressive.

Although MRI scans of VaD patients were positive for subcortical infarction, these lesions tended to be small. By contrast, all patients with VaD presented with a considerable degree of leukoaraiosis. More importantly, there was no difference in LA scores among patients diagnosed by the separate VaD diagnostic schemes, and all patients with VaD displayed LA scores many times higher than those of patients with AD. Significant differences were also found with respect to vascular risk factors such that hypertension and heart disease was significantly greater in the VaD group than in the AD group. Furthermore, hypertension was by far the most prevalent risk factor associated with VaD. Despite the diagnostic scheme applied, the relative proportion of patients with hypertension, diabetes, or evidence of heart disease was basically the same as

for the vascular group as whole. Thus, despite the diagnostic inconsistency among the VaD schemes discussed above, neuroradiological evidence of LA and certain vascular risk factors were consistently present across the different diagnostic schemes for VaD, and therefore may serve as indicators of vascular, rather than AD pathology.

With respect to the neuropsychological data, neuropsychological assessment was not able to differentiate between the various diagnostic schemes for VaD. Regardless of the diagnostic scheme used, patients with VaD presented with differentially lower scores on tests of mental set and visuoconstruction, while patients with AD were particularly disadvantaged on tests of lexical/semantic knowledge and delayed recognition memory. Moreover, the neuropsychological data revealed a striking double dissociation. Specifically, patients diagnosed with VaD by any of the schemes obtained test scores that were 1–2 standard deviations higher within the domains of lexical/semantic knowledge and delayed recognition memory. The opposite relationship was seen within the domains of mental set and visuoconstruction where the scores of patients with AD far exceeded those of the patients diagnosed with VaD, regardless of the diagnostic scheme under consideration.

Does Pure Vascular Dementia Really Exist?

Recent clinical-pathological data suggest that *pure* vascular dementia is rare. A variety of studies have shown that patients clinically diagnosed with AD exhibit neuropathologic evidence of cerebrovascular alterations, while patients clinically diagnosed with VaD exhibit both senile plaques and neurofibrillary tangles upon autopsy (Bowler, Munoz, & Hachinski, 1998; Crystal et al., 2000; Nolan, Lino, Seligmann, & Blass, 1998; Victoroff, Mack, Lyness, & Chui, 1995).

Snowden and Markesbery (1999) research suggests that cerebrovascular alterations in the brain are capable of modifying the pathological presentation of AD. For example, while there was a very low incidence of VaD among participants in the *nun study*, patients who met pathological criteria for AD *and* exhibited pathological evidence of cerebrovascular alterations had *fewer* senile plaques and neurofibrillary tangles, than did AD patients whose brains contained no evidence of cerebrovascular disease. Nagy et al. (1997) have presented similar findings. Other research findings suggest that the presence of AD pathology can influence the presence of vascular pathology. Specifically, the accumulation of beta amyloid seen in AD can frequently infiltrate cerebral vasculature (cerebral amyloid angiopathy), resulting in chronic hypoperfusion (Kalaria & Ballard, 1999). While it seems that both pathologies are capable of modifying each other, it is difficult to determine the degree of modification and the relative effect each type of neuropathology has upon the other.

Despite the evidence that multiple neuropathological substrates might underlie the clinical presentation of dementia among some patients, Libon et al. (2001) have demonstrated that *independent* of clinical diagnosis, periventricular and deep white matter alterations on MRI are uniquely associated with a pattern of neuropsychological deficits characteristic of subcortical, rather than cortical dementia. Furthermore, Gunning-Dixon and Raz (2000) recently conducted a meta-analysis of studies examining the effect of MRI leukoaraiosis on neuropsychological functioning among participants who were not demented. Similar to the neuropsychological data reported above, they found that leukoaraiosis on MRI was associated with poorer performance on tests of processing speed, delayed recognition memory, and executive control.

Diagnosing Versus Describing the Dementias

Recently, Sachdev (2000) posed the rhetorical question, ''Is it time to retire the term dementia?'' This suggestion was based on the disparities with which patients are diagnosed with dementia, and the frequent autopsy evidence of multiple neuropathologies that may be associated with dementing illnesses. Similarly, Groves et al. (2000) have recently challenged the usefulness of vascular dementia as a general diagnosis. In comparing the clinical differences among patients with AD and VaD, few differences were found. They concluded that the current use of the construct of 'vascular dementia' may be too liberal to be meaningful, and very likely represents multiple entities, rather than a single nosological entity. Furthermore, Groves et al. (2000) suggest that an alternative

means of characterizing vascular dementia is to constitute vascular subgroups in terms of disease mortality, cognition, functional decline, and behavior disturbances (p. 312). For these reasons Bowler and Hachinski (1995) have proposed the term *vascular cognitive impairment* (VCI) as a more accurate way to describe the association between neuropsychological deficits and cerebrovascular alterations.

Our findings support a re-characterization of the vascular dementia process. The discrepancy among the VaD diagnostic schemes, and the inconsistent neuropathological verification of diagnoses suggests that the current methods of diagnosis are insufficient. Thus, we propose an alternate way to characterize the contribution of vascular disease, integrating all available clinical information along a multi-dimensional system. Our goal is to provide a comprehensive *description* of a patient's clinical presentation. In particular we suggest that careful consideration be given to patients' performance on neuropsychological tests, in addition to data derived from other sources, such as neuroimaging, vascular risk factors, and behavioral/emotional disturbances. The following 3-criterion system is proposed as a means of describing the various presentations of dementia with respect to clinical findings that may be useful in distinguishing AD from vascular dementia.

Criterion One (Neuropsychological Functioning)

To what degree does the patient exhibit an amnestic versus an executive control syndrome upon neuropsychological examination? As described above, the administration of a brief, but comprehensive neuropsychological protocol often yields striking dissociations. If, for example, performance on tests of mental set/executive control and visuoconstruction are markedly impaired as compared to performance on tests of lexical/semantic knowledge and delayed recognition memory, this might constitute strong evidence that vascular pathology is involved in the aetiology of the dementia.

Criterion Two (Neuroradiology)

Recently, great strides have been made in the development of methods that can quantify the severity of white matter, as well as gray matter alterations as seen on MRI scans. However, in developing such scales, attention should be paid to their psychometric properties. Optimally, such scales should not suffer from a restriction of range, and data should be measurable on an interval level scale. The Junque Leukoaraiosis Scale fulfills these requirements. The reason we have used this scale to operationally define periventricular and deep white matter alterations is that its psychometric properties permit the scale to be used as either a dependent or independent variable (Libon et al., 1998). Similar scoring systems measuring alterations in gray matter need to be developed. Thus, a combination of neuropsychological assessment as described above, along with radiological scales that contain sound psychometric properties may allow for statistical algorithms by which to operationally define dementia subgroups.

On the basis of the data presented above, a Leukoaraiosis scale of 10 or greater, that is, involving at least 25% of the subcortical white matter, in conjunction with striking impairment on tests of mental set/visuoconstruction would strongly suggest that vascular pathology is exercising a differential effect with respect to the clinical expression of a dementing illness. Alternatively, a very high score on the leukoaraiosis scale, along with significant impairment on tests of mental set/executive control and delayed recognition memory might suggest that white matter, as well as gray matter pathology, are equally important in understanding the clinical expression of the dementing illness.

Criterion Three (Vascular Risk Factors)

Here, vascular risk factors such as hypertension, heart disease, diabetes, as well as other co-morbid medical conditions such as incontinence and gait disorder should be considered. Behavioral disturbances (Cummings, 1997), which are common in all types of dementia could be coded here.

This paradigm is not intended to replace any of the existing diagnostic schemes, but rather to strengthen their diagnostic certainty. Also, we make no claims that the tests or methods used in the present research are the optimal means to address the questions under consideration. However, the paradigm described above is a means by

which one can measure the relative contribution of various behavioral and neuropsychological disturbances observed in a dementing illness, and understand how these disturbances might be related to specific neuropathological alterations. Ultimately, our goal is to assess the extent to which a patient exhibits evidence of one or multiple neuropathologies. In this respect, such a paradigm may be useful in measuring the *relative contribution* of various pathological processes regarding the clinical presentation of a dementing illness.

AD and VaD are major public health problems. The paradigm described above is suggested in order to achieve greater diagnostic specificity. The urgency to work toward this goal is, perhaps, underscored by the fact that medication for dementia is now available. Clearly, a goal for the future is to conduct research to devise methods by which neuroradiological and neuropsychological data can be combined in order to better predict response to treatment.

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APPENDIX: THE WORD LIST GENERATION 'ANIMAL' ASSOCIATION INDEX

For the purpose of illustrating the calculation of the 'animal' association index the appendix shows the seven 'animal' word list generation responses generated by a dementia participant. Starting with the second response and moving across the page, ''mule'' matches with the first response, ''horse'' on six attributes (*big, local, farm, herbivore, mammal & equine*). The third response is ''lion,'' which matches with ''mule'' on only two attributes (*big & mammal*). After the number of shared attributes for each successive response pair is tabulated, the total sum of shared attributes is obtained for all successive responses. Thus, the total sum of shared attributes is 22. The AI is calculated by dividing the sum of shared attributes by the number of responses minus one, because the attributes of the first response are never actually figured into the sum. The AI for this patient is 3.67 or $22/(7-1)$. As can be seen from this example, the AI provides a measure of the semantic association among all consecutive 'animal' word list generation responses, and is independent of the number of responses generated.