Classification of vascular dementia in the Cardiovascular Health Study Cognition Study

O.L. Lopez, MD; L.H. Kuller, MD; J.T. Becker, PhD; W.J. Jagust, MD; S.T. DeKosky, MD; A. Fitzpatrick, PhD; J. Breitner, MD; C. Lyketsos, MD; C. Kawas, MD; and M. Carlson, PhD

Abstract—*Objective:* To describe the diagnostic classification of subjects with incident vascular dementia (VaD) participating in the Cardiovascular Health Study (CHS) Cognition Study. *Methods:* The CHS classified 480 incident cases between 1994 and 1999 among 3,608 CHS participants who had brain MRI in 1992 through 1994 and in 1997 through 1998. The patients were diagnosed before and after reviewing the brain MRI. *Results:* The pre-MRI classification showed that 52 participants had VaD and 76 had both Alzheimer disease (AD) and VaD. The post-MRI classification showed that the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV) criteria classified 61 subjects as having VaD, the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria classified 43 subjects as having probable VaD and 10 as possible VaD, and the State of California Alzheimer's Disease Diagnostic and Treatment Center (ADDTC) criteria classified 117 as having probable VaD and 96 as possible. The combination of the ADDTC and National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria was used to examine the spectrum of vascular disease in dementia. The dementia was attributable to only vascular factors in 56 cases (probable VaD); VaD coexisted with AD in 61 cases, although the VaD component was the leading cause of dementia (probable VaD with AD); AD was the leading cause of dementia in 61 cases (possible VaD and probable AD); and in 29 cases, it was not clear that either AD or VaD was the primary diagnosis (possible AD and possible VaD). *Conclusions:* None of the clinical criteria for VaD identified the same group of subjects. The diagnosis of vascular dementia is difficult in epidemiologic studies because poststroke dementia can be due to Alzheimer disease (AD) and evidence of vascular disease can be found in the MRI of dementia cases without clinical strokes. Whether the clinical progression is related to AD pathology or vascular disease is difficult to establish.

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Clinical[1,2] and neuropathologic[3,4] studies have shown that vascular dementia (VaD) is the second most frequent cause of dementia after Alzheimer disease (AD). However, the diagnosis of VaD is complex, and the heterogeneity of its clinical presentation and progression has led to debate. It is traditionally recognized that VaD develops after a single or multiple clinical strokes and that it can have a stepwise progression.[5] However, VaD can occur in subjects without clinical strokes, and it can have a gradually progressive course.[6,7] Furthermore, approximately half of the patients with clinically diagnosed VaD have concomitant AD at autopsy.[8,9]

Several diagnostic criteria have been proposed for the clinical diagnosis of VaD (e.g., Diagnostic and Statistical Manual of Mental Disorders, 4th ed. [DSM-IV],[10] the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences [NINDS-AIREN],[11] the State of California Alzheimer's Disease Diagnostic and Treatment Centers [ADDTC] criteria for VaD,[12] and International Classification of Diseases, 10th ed. [ICD-10]).[13] The operationalized version of these criteria attempts to capture the wide spectrum of clinical and radiologic presentation of VaD. However, clinicopathologic

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From the Departments of Neurology and Psychiatry (Drs. Lopez, Becker, and DeKosky), University of Pittsburgh School of Medicine, and Department of Epidemiology (Dr. Kuller), University of Pittsburgh Graduate School of Public Health, PA, University of California at Berkeley (W.J. Jagust), Department of Biostatistics (Dr. Fitzpatrick), University of Washington, and Geriatric Research, Education, and Clinical Center (Dr. Breitner), Veterans Administration Puget Sound Health Care System, Seattle, WA, Department of Psychiatry (Dr. Lyketsos), Johns Hopkins University, and Johns Hopkins Bloomberg School of Public Health (Dr. Carlson), Baltimore, MD, and Department of Neurology (Dr. Kawas), University of California, Irvine.

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Address correspondence and reprint requests to Dr. O.L. Lopez, 3501 Forbes Ave., Oxford Bldg., Suite 830, Pittsburgh, PA 15213; e-mail: lopezol@msx.upmc.edu

studies have shown that they have low sensitivity with high specificity,[4,14] and the concomitant use of the NINDS-AIREN, DSM-IV, and ICD-10 criteria in selected series has shown that they overlapped only in <50% of the cases.[15] Furthermore, reliability studies of the operationalized neuroimaging guidelines proposed by the NINDS-AIREN criteria have shown poor to good degree of agreement among expert radiologists.[16]

These issues have direct consequences in population studies; the incidence and prevalence of VaD will depend on the criteria used for its identification.[17] The Cardiovascular Heath Study (CHS) Cognition Study has classified the cases with VaD with three diagnostic classifications (i.e., NINDS-AIREN, DSM-IV, ADDTC) and has used the ADDTC criteria in association with the National Institute of Neurological and Communication Disorders and Stroke (NINCDS)-Alzheimer's Disease and Related Disorders Association (ADRDA)[18] to examine cases where the vascular component of the dementia was less clear. Furthermore, because the majority of the epidemiologic studies based the diagnosis of VaD on the history of stroke,[19-21] the CHS Cognition Study has classified the cases before and after the review of the neuroimaging studies. This allowed us to compare and contrast the diagnosis of VaD based solely on history of strokes or severe vascular disease vs that aided by neuroimaging.

The risk factors for VaD in the CHS Cognition Study were examined in a companion article. The risk factors for VaD were evaluated according the different available criteria for VaD (i.e., NINDS-AIREN, DSM-IV, ADDTC) and by pre-MRI classification.

Methods. In 1988 through 1989, 5,201 noninstitutionalized individuals over age 65 were recruited from four communities using the Part A Medicare list (Pittsburgh, PA, Sacramento, CA, Winston-Salem, NC, and Hagerstown, MD). The mean age of the cohort in 1989 to 1990 was 72 years. In 1992 to 1993, the third year of the study, 687 African Americans were added to the study in the same manner in three of the four centers. Their mean age in 1992 was 71 years. The demographic characteristics of the total cohort of 5,888 participants have been described previously.[22]

All participants were examined annually at their clinics from 1988 through 1999 with the Modified Mini-Mental State Examination (3MSE)[23] and the Digit Symbol Substitution Test (DSST)[24] and had 6-month interview telephone calls. We attempted to obtain cognitive information using the Telephone Interview for Cognitive Status (TICS) for individuals who did not come to the clinic.[25] The participants were also assessed with the Benton Visual Retention Test (BVRT) from 1994 to 1999.[26] Further information on cognition was obtained from proxies using the Informant Questionnaire for Cognitive Decline in the Elderly (IQ-CODE)[27] and from physicians for participants who had died or who were unable to complete the 3MSE or TICS.

The CHS staff obtained information regarding all overnight hospitalizations including face sheets, discharge diagnosis, and history and physical exam results. For any possible cardiovascular/cerebrovascular diagnoses and for all deaths, detailed reviews were completed from the entire record, including procedures. An adjudication committee for cardiovascular disease and deaths and a separate committee for stroke evaluated the specific cardiovascular disease and stroke endpoints of the study. During most of the study, the CHS staff also obtained information from participants and next of kin regarding the circumstances of the illness and history of dementia.

Information regarding vision and hearing was also obtained as well as functional status using instrumental activities of daily living (IADLs)[28] and activities of daily living (ADLs).[29] Pharmaceutical drug use was collected in considerable detail at yearly intervals, including use of drugs to treat depression and dementia, anti-inflammatory agents, hormones, and antihypertensive drug therapy. Data on alcohol consumption were also collected. In 1992 to 1994, 3,608 participants had a brain MRI; repeat MRI was done in 2,112 participants during 1997 to 1998.

In 1998 to 1999, the CHS attempted to identify all participants who had either prevalent dementia at the time of the MRI exam in 1992 through 1994 or subsequent incident dementia to 1998 to 1999. The sample was limited to those participants who had an MRI in 1992 to 1994, for a total of 3,608 participants. Comparison of those who did and did not have MRI has previously been reported.[30,31] The methodology used in the CHS Cognition Study is described elsewhere.[22,32]

The 3,608 participants were first divided into groups for high and low risk of possible dementia based on the previous cognitive testing, changes in cognitive scores, nursing home admission, and history of stroke. Participants were classified at high risk for dementia if they had any of the following characteristics: 1) 3MSE score of <80 at one of their last two clinic visits in the study, 2) a 5-point decline in the 3MSE from the time of MRI to last contact, 3) a TICS score of <28,[25] 4) an IQ-CODE score of >3.6, 5) incident stroke, 6) currently residing in a nursing home, or 7) dementia diagnosis found on medical record review. The medical record review was not limited to hospital discharge diagnoses.

The overall study design was a modified three-stage screening procedure. In three of the clinics, only the high-risk white individuals, but all of the African Americans, were then subjected to detailed evaluation for the diagnosis of dementia. This was done to increase the power of the analysis within the African American group to increase the overall power of the study. The examination of all the Pittsburgh participants allowed us to estimate the "misses" among the low-risk participants at the other centers.

The MRI evaluations have been described previously.[30,31,33] In brief, a cerebral infarct was defined as an area of abnormal signal in a vascular distribution that lacked mass effect. Infarcts in the cortical gray and deep nuclear regions had to be brighter on spin density and T2-weighted images than normal gray matter. Infarcts in the white matter were similarly defined except that they had to be hypodense in T1-weighted images to distinguish them from diffuse white matter disease. For the purpose of this study, we present the MRI-identified infarcts detected in the MRI done from 1992 to 1994.

Symptoms of depression were measured with the modified version of the Center for Epidemiology Studies Depression Scale (CES-D) 10-item version from 1992 to 1999, and scores of >7 have shown increased risk for depression in elderly subjects.[34] In 1998 to 1999, we administered the Neuropsychiatric Inventory (NPI).[35] Details of the neurologic exam have been published previously.[22] The neurologic exam also included the Unified Parkinson's Disease Rating Scale[36] and the Hachinski Rating Scale (HRS),[37] total and modified scores.[38]

The characteristics of the CHS neuropsychological battery have been published previously.[22] In brief, the neuropsychological battery included the following tests: premorbid intelligence: the American version of the National Reading Test[39] and Raven's Colored Progressive Matrices (modified)[40]; memory: California Verbal Learning Test (CVLT)[41] and modified Rey–Osterreith figure[42]; language: Boston Naming Test[43] and Verbal Fluency Test[44]; visuoperceptual/visuoconstructional: Block Design (from the Wechsler Adult Intelligence Scale–Revised)[24] and modified Rey–Osterreith figure[42]; executive functions: Stroop Neuropsychological Screening Test,[45] Trail Making,[46] Digit Spans,[24] and Baddeley and Papagno Divided Attention Task[47]; motor: Grooved Pegboard Test.[48] The results of the neuropsychological battery were classified as normal or abnormal based on normative data collected from a sample of 250 unimpaired subjects in Pittsburgh. For the purpose of this study, we present the neuropsychological characteristics of all incident cases who provided scores in all neuropsychological measures (n = 243).

The neuropsychological test data were transformed into standardized scores using routine procedures. The subjects were stratified by age (+80 years) and education (+ high school education), and the individual test scores were z transformed based on the appropriate mean and SD from the control subjects. All scores

were then converted into T scores ($T = z*10 + 50$). This results in a mean T of 50 for the control subjects, with a SD of 10. These T scores are then interpreted using established standards.[49] Thus, T scores below 40 were considered mildly impaired, scores below 30 were moderately impaired, and those under 20 were severely impaired.

The neuropsychological differences between VaD subgroups were explored with composite scores of the T scores: verbal memory: CVLT trial 1, Trail 5, trials 1 to 5, and total free recall (long); nonverbal memory: Immediate and Delay Recall of the modified Rey–Osterreith figure; visuospatial: Raven's Colored Progressive Matrices, Block Design, and copy of the modified Rey–Osterreith figure; language: Boston Naming Test, fluency (letter), and category; executive: Trail Making B, Trail Making B/A, Stroop Test (interference), and Baddeley and Papagno (percentage of change in lists); attention: Digit Span Forwards and Backwards; and fine motor control: Grooved Pegboard, dominant and nondominant time.

Diagnostic classification. Participants classified as demented were reviewed by an adjudication committee comprising experts in dementia diagnosis. The adjudication committee had access to the historical CHS cognitive test scores, primarily the 3MSE (and subscales), DSST, BVRT, and TICS, as well as the depression scores, vision and hearing testing, history of alcohol intake, IADL questionnaire, IQ-CODE, dementia questionnaire (DQ),[50] vital status, date of death, history of hospitalizations, treatments and drugs to treat dementia, results of the current neuropsychological assessment, MRI scans (1992 to 1994 and 1997 to 1998), the neurologic exam, NPI and CES-D, and recent hospital records. Based on the information available, the adjudication committee classified all CHS participants, including those who were dead in 1998 to 1999.

The diagnosis of dementia was based on a deficit in performance in two or more cognitive domains that were of sufficient severity to affect the subjects' ADLs and history of normal intellectual function before the onset of cognitive abnormalities. An abnormal domain was present when at least two tests of the same domain were abnormal. The dementia criteria were designed to identify subjects with syndromes that could include relatively preserved memory functions (e.g., frontotemporal dementia), and thus a memory deficit was not required for the diagnosis of dementia. This clinical diagnosis of dementia has been successfully used over the last two decades, and it has shown 98% sensitivity and 88% specificity for AD.[51] The diagnosis of dementia was independent of the MRI findings, although the MRI was used to classify different dementia types.

The diagnosis of VaD was done first without MRI data, where the clinicians provided a diagnosis based on the clinical evidence: non-VaD, VaD, or mixed (VaD with AD, or other cause of dementia). In a second step, the adjudication committee applied a set of diagnostic criteria to classify VaD: DSM-IV, ADDTC, and NINDS-AIREN. The most relevant characteristics of each set of criteria are shown in table 1.

The ADDTC criteria were used in association with the NINCDS-ADRDA criteria for AD[18] to better identify the AD component in cases with severe cerebrovascular disease. These participants were classified in four groups: 1) probable VaD: the clinical symptoms are clearly related to cerebrovascular disease; 2) probable VaD and AD: there is a clear relationship between clinical symptoms and cerebrovascular disease, but the clinical course or the neuropsychological testing indicated a possible AD process; 3) possible VaD and probable AD: AD symptoms are the main manifestation of the dementia syndrome, with a less clear relationship between clinical symptoms and cerebrovascular disease; and 4) possible VaD and possible AD: AD and VaD symptoms were present, but it was not clear that either VaD or AD was the primary diagnosis. The CHS normal subjects were compared and contrasted only with the four groups obtained from the concomitant use of the ADDTC and NINCDS-ADRDA criteria. The CHS database does not include assessments of urinary incontinence. Therefore, this was not taken into consideration for the diagnosis of possible VaD.

The onset of dementia was determined by the adjudication committee based on the longitudinal and qualitative changes in the 3MSE, DSST, and BVRT scores as well as on the proxy report from the DQ and IQ-CODE.

Statistical analysis. Group differences were analyzed with χ^2 test, t test, and analysis of variance. The level of agreement between diagnostic criteria was calculated using the κ statistics. The interpretation of the level of agreement was as follows: slight: 0.0 to 2.0; fair: 0.20 to 0.40; moderate: 0.40 to 0.60; substantial: 0.60 to 0.80; almost perfect: 0.80 to 1.0.[52]

Results. The CHS Cognition Study has identified 480 incident dementia cases from 1994 to 1999. Because the purpose of the study was to determine the VaD classification with and without MRI, we first examined the characteristics of the subjects classified as having VaD before reviewing the MRI, and later we applied three diagnostic classifications (i.e., DSM-IV, ADDTC, NINDS-AIREN) using MRI data. The incidence of dementia was 16.3 per 1,000 persons among the 3,608 participants, and the incidence of VaD was 3.8 per 1,000 persons by pre-MRI diagnosis over the 5.4 years of follow-up.

The pre-MRI diagnosis classified 352 cases as non-VaD, 76 as mixed, and 52 as VaD. The DSM-IV criteria classified 416 cases as non-VaD and 61 cases as VaD. The ADDTC criteria classified 264 cases as non-VaD, 117 as probable, and 96 as possible. The NINDS-AIREN criteria classified 423 subjects as non-VaD, 43 as probable VaD, and 10 as possible VaD. The age, education level, gender, and 3MSE and DSST scores at baseline MRI in 1992 to 1994, the annual change in 3MSE scores from dementia onset to last contact, total and modified HRS scores, ADLs, IADLs, CES-D score of >8, and prevalence and incidence of strokes in subjects identified with each clinical criteria can be found in tables E-1 and E-2 on the *Neurology* Web site at www.neurology.org.

ADDTC and NINCDS-ADRDA criteria. The simultaneous use of the ADDTC and NINCDS-ADRDA criteria produced five distinct groups of subjects. In two, non-VaD (mainly AD cases, n = 264) and VaD (probable VaD, n = 56), diagnosis occurred in isolation. In three of the groups, AD and VaD features were present. In two of these groups, the differences were characterized by the degree of certainty of the AD or VaD diagnosis (probable VaD and AD, n = 61; possible VaD and possible AD, n = 29). However, it was the fifth group (possible VaD and possible AD, n = 61) that produced the most diagnostic uncertainty. In these cases, it was virtually impossible to disentangle the independent contributions of the two disorders.

Table 2 shows the age, education level, gender, 3MSE, and DSST scores at baseline MRI in 1992 to 1994, the annual change in 3MSE scores from dementia onset to last contact, total and modified HRS scores, ADLs, IADLs, CES-D score of >8, and prevalence and incidence of strokes. Nondemented subjects, at baseline and at last contact, had higher 3MSE and DSST scores than the dementia groups. The 3MSE score at last clinic visit and its annual rate of change were worse in subjects with probable VaD and AD and possible AD and probable AD compared with those with non-VaD, probable VaD, and possible VaD and possible AD. There were more subjects with dementia who reported at least one abnormal ADL or IADL compared with nondemented subjects. The HRS (total and modified) scores were higher in probable VaD than in the other groups. However, normal and non-VaD subjects had lower HRS scores than the VaD groups. Prevalent and incident strokes were more frequent in subjects with probable VaD compared with normal subjects and other dementia groups.

Table 1 *Key components of the NINDS-AIREN, ADDTC, and DSM-IV criteria*

	NINDS-AIREN: required	ADDTC: required	DSM-IV: required
Dementia			
Dementia criteria specified	Yes	N/S	Yes
Memory impaired and deficits in two other cognitive domains (ICD-10)	Yes	N/S	No
Memory impaired and deficits in one other cognitive domain	No	N/S	Yes
Cognitive deficit must not be isolated to a narrow category of intellectual performance	Implied	Specified	Implied
Cognitive deficits must interfere with activities of daily living	Yes	Yes	Yes
Relationship with AD and other disease processes			
Specifically rule out presence of Alzheimer disease or other diseases that in and of themselves could account for deficits in memory and cognition	Yes	N/S	N/S
Exclude cases with delirium	Yes	Yes	Yes
Patients can present with superimposed psychosis or depression	No	No	Yes
Focal neurologic signs and symptoms			
Presence of specific focal signs consistent with stroke on neurologic examination (hemiparesis, Babinski sign, pseudobulbar palsy, sensory deficits, or other focal motor/sensory deficit)	Yes	N/S	Yes
Neuroimaging			
CT and MRI evidence of CVD that is judged to be etiologically related to cognitive disturbance	Yes	Yes	Yes
CT and MRI evidence of large multiple infarcts	Yes	Yes	Yes
CT and MRI evidence of infarcts in specific vascular distributions (e.g., single strategically placed infarct in the angular gyrus, basal forebrain, or ACA or PCA territories, multiple basal ganglia lacunes, or white matter lacunes)	Yes	N/S	N/S
CT and MRI evidence of extensive periventricular white matter lesions	Yes	N/S	N/S
Relationship between CVD and cognitive deficits			
Onset of dementia within 3 mo or a clear relationship between stroke and dementia	Yes	Yes	Yes
Abrupt deterioration in cognitive functions	Yes	Yes	Yes
Fluctuating, stepwise progression of cognitive deficits	Yes	Yes	Yes
Insidious onset and gradual progression can be encountered	No	No	Yes
History of TIAs	No	Yes	No

NINDS-AIREN = National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences; ADDTC = State of California Alzheimer's Disease Diagnostic and Treatment Centers; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders (4th ed.); N/S = not specified; ICD-10 = International Classification of Diseases (10th ed.); AD = Alzheimer disease; CVD = cerebrovascular disease; ACA = anterior cerebral artery; PCA = posterior cerebral artery.

For illustrative purposes, we present in this study the neuropsychological characteristics of all incident cases who provided scores in all neuropsychological measures (n = 243).

The *T* scores of the VaD subgroups are shown in table 3. Subjects with probable VaD had worse visuospatial and fine motor control performance than those with the diagnosis of probable VaD with AD, possible VaD with probable AD, and possible VaD with possible AD. No statistical differences among groups were noted in terms of memory, language, or executive functions.

Criteria agreement. Table 4 shows the relationship among different criteria. The κ statistics ranged from 0.21 (ADDTC vs NINDS-AIREN) to 0.76 (NINDS-AIREN vs DSM-IV). The disagreement among the criteria stems from three sources: 1) the apparent abrupt onset of the symptoms in cases with no cerebral infarcts or severe white matter lesions (e.g., pre-MRI vs NINDS-AIREN vs ADDTC); 2) the relatively gradual onset of symptoms with severe cerebrovascular disease in MRI studies (e.g., ADDTC vs NINDS-AIREN vs pre-MRI vs DSM-IV); 3) the dementia criteria (e.g., ADDTC vs NINDS-AIREN vs DSM-IV). Of the 132 subjects with the pre-MRI diagnosis of VaD (alone or mixed), only 38 were classified as VaD by the three diagnostic criteria. In addition, the three diagnostic criteria agreed in the diagnosis of VaD in 45 cases.

Discussion. Although the percentage of incident cases identified with each diagnostic classification was similar (pre-MRI VaD: 11%; DSM-IV: 13%; NINDS-AIREN probable VaD: 9%; ADDTC and

Table 2 *Descriptive statistics for normal (not MCI) and incident dementia participants classified according to ADDTC criteria for VaD and NINCDS/ADRDA criteria for AD*

	Normal, not MCI	Non-VaD*	Probable VaD	Probable VaD with AD	Possible VaD with probable AD	Possible VaD with possible AD	IC
No. of subjects (% of incident cases)	2318	262 (55)	56 (12)	61 (13)	29 (6)	61 (14)	
Age at MRI in 1992–94, y	74.0 ± 4.4	77.7 ± 5.5	76.8 ± 4.5	78.5 ± 5.5	78.5 ± 5.2	79.4 ± 5.7	B, C
Age at last contact, y	79.0 ± 4.3	82.4 ± 5.5	81.1 ± 4.9	83.1 ± 5.4	83.2 ± 5.2	83.9 ± 5.9	B, C
Modified Mini-Mental State Examination							
At MRI in 1992–94	93.1 ± 5.0	88.1 ± 7.3	88.0 ± 7.9	89.7 ± 6.1	88.7 ± 6.2	88.4 ± 6.6	B, C
At dementia onset		80.4 ± 9.7	81.6 ± 13.3	80.9 ± 10.8	79.0 ± 10.6	82.3 ± 6.7	C
At last contact	94.2 ± 6.1	69.3 ± 18.1	72.2 ± 19.6	65.0 ± 18.8	59.7 ± 26.7	69.2 ± 20.8	B, D
Annual change from dementia onset to last contact	—	−6.9 ± 10.4	−5.6 ± 15.9	−9.7 ± 8.1	−13.3 ± 18.6	−8.3 ± 9.5	D
Digit Symbol Substitution Test							
At MRI in 1992–94	43.7 ± 11.9	31.5 ± 12.0	31.3 ± 12.7	32.8 ± 11.3	28.7 ± 11.2	29.9 ± 11.0	B, C
At last contact	40.6 ± 12.4	22.4 ± 11.5	21.3 ± 9.8	21.6 ± 11.8	19.5 ± 11.1	21.1 ± 10.3	B, C
Education level							
<high school (%)	1,123 (49)	156 (60)	34 (61)	33 (54)	15 (52)	34 (56)	F
Gender							
Females (%)	1,367 (59)	168 (64)	26 (46)	30 (49)	18 (62)	38 (62)	F
Race							
African American (%)	216 (9)	45 (17)	10 (18)	11 (18)	6 (21)	4 (7)	F
HRS at last contact							
Total score	1.2 ± 1.5†	1.8 ± 1.7	6.6 ± 4.0	3.7 ± 4.3	3.0 ± 3.4	3.1 ± 2.8	A
Modified score	.83 ± 1.3†	.83 ± 1.4	5.2 ± 3.4	2.5 ± 3.4	2.4 ± 3.0	2.2 ± 2.4	A, E
CES-D score >8 at last contact (%)	624 (27)	103 (40)	30 (56)	19 (32)	10 (36)	25 (42)	B, C
Subjects with at least one IADL impaired at last contact (%)	777 (34)	139 (54)	36 (64)	31 (51)	16 (57)	30 (50)	B, C
Subjects with at least one ADL impaired at last contact (%)	474 (22.5)	89 (35)	27 (48)	26 (43)	9 (32)	27 (45)	B, C
Prevalent stroke (%)	86 (4)	3 (1)	15 (27)	6 (10)	2 (7)	12 (20)	F
Incident stroke (%)	85 (4)	13 (5)	26 (63)	13 (24)	6 (22)	17 (35)	A

A = probable VaD different from the other four dementia groups, and normal subjects; B = normal subjects different from dementia cases; C = no differences among dementia cases; D = non-VaD, probable VaD, probable VaD with AD, and possible VaD with possible AD different from possible VaD with probable AD; E = normal subjects and non-VaD different from probable VaD, probable VaD with AD, possible VaD with probable AD, and possible VaD with possible AD; F = no statistical differences among groups.

* Two hundred forty-three were Alzheimer disease.
† Five hundred sixty normal cases.

MCI = mild cognitive impairment; ADDTC = State of California Alzheimer's Disease Diagnostic and Treatment Centers; VaD = vascular dementia; NINCDS = National Institute of Neurological and Communication Disorders Stroke; ADRDA = Alzheimer's Disease and Related Disorders Association; AD = Alzheimer disease; HRS = Hachinski Rating Scale; CES-D = Center for Epidemiological Studies–Depression Scale; IADL = instrumental activity of daily living; ADL = activity of daily living.

NINCDS-ADRDA probable VaD: 12%), except for the ADDTC (probable VaD: 24%), none of these diagnostic classifications identified the same cohort. These findings are similar to previous studies that found poor agreement among different diagnostic schemes.[53] However, there are two issues that made our results different. First, all demented and nondemented subjects were examined with a standardized

Table 3 *Neuropsychological characteristics of subjects with VaD: composite scores (*T *scores)*

	Non-VaD	Probable VaD, not AD	Probable VaD with AD	Possible VaD with probable AD	Possible VaD with possible AD	IC
No. of cases	156	26	28	15	18	
Cognitive domain						
Verbal memory	32.0 ± 8.6	31.4 ± 9.1	28.4 ± 7.1	32.4 ± 5.2	30.4 ± 6.9	B
Nonverbal memory	29.9 ± 10.6	27.0 ± 7.7	30.1 ± 10.4	26.5 ± 6.7	24.2 ± 9.3	B
Language	30.1 ± 9.9	27.0 ± 10.5	30.3 ± 10.2	32.3 ± 10.8	28.0 ± 8.9	B
Visuoconstructional	31.2 ± 10.3	22.8 ± 10.0	32.7 ± 8.4	26.1 ± 8.3	25.3 ± 13.6	A
Executive functions	34.1 ± 12.6	33.3 ± 12.6	32.6 ± 11.4	26.6 ± 13.6	33.2 ± 20.0	B
Fine motor control	31.8 ± 15.3	19.3.0 ± 18.0	25.6 ± 14.2	30.7 ± 14.8	21.7 ± 10.9	A

Intergroup comparison (IC): A = probable vascular Dementia (VaD) different from probable VaD with AD, possible VaD with probable AD, possible VaD with possible AD, and non-VaD; B = no statistical differences.

MRI protocol. This is an important distinction from other hospital- or population-based studies, where only subjects with clinical strokes had neuroradiologic assessments. Second, extensive premorbid longitudinal clinical information was available to determine the progressive nature of the vascular and cognitive symptoms. This allowed us to examine the relationship between dementia and vascular disease.

The discrepancies in the frequency estimates among different diagnostic criteria for VaD have been reported in population- and stroke clinic–based studies. A hospital-based study found that the DSM-IV criteria for VaD identified 21% of the subjects with poststroke dementia, whereas the NINDS-AIREN criteria identified 6%.[17] Following a stroke, 52% of patients met the DSM-IV criteria for VaD, 33% met the ICD-10 criteria, 27% the ADDTC criteria, and 14% the NINDS-AIREN criteria for VaD.[15] In a Japanese population, 19% of the patients with clinical strokes who were examined with MRI studies met the DSM-IV criteria for VaD, 19% the NINDS-AIREN, and 31% the ADDTC criteria for VaD.[54] These results are consistent with the trend found in this study: The ADDTC criteria tend to identify more VaD cases than the DSM-IV and NINDS-AIREN. However, they are difficult to compare with ours, as these studies did not have longitudinal premorbid data, which are essential to rule out an AD progressive pattern.

The concept of VaD is based on a history of a clinical stroke, which is assumed to be the only etiology of the cognitive deficits.[11,12] However, only 29% of the cases identified as pre-MRI VaD were classified as VaD by any of the post-MRI criteria. Abrupt changes in cognition, in the context of severe cardiovascular disease, without MRI correlates and the presence of significant MRI vascular disease without clinical strokes are the major discrepancies between pre- and postneuroimaging assessment. A clinicopathologic study found that only half of the subjects with radiologic evidence of critical ischemic lesions had history of clinical stroke or focal motor deficits.[55] This is particularly important because the diagnosis of VaD is sometimes made only in subjects with history of strokes. Therefore, stroke patients with subsequent cognitive deterioration may represent one extreme of VaD, where vascular disease is more severe.

The fact that there are subjects with abrupt onset of dementia associated with focal motor and sensory deficits and others without any indication of these deficits but with evidence of severe cerebrovascular disease from MRI studies can be a factor of discrepancy among different clinical criteria. This may explain the fact that the highest diagnostic agreement was between the DSM-IV and NINDS-AIREN criteria. These two criteria required the presence of abrupt onset of cognitive deficits, in the context of focal neurologic signs and symptoms, following a clinically suspected stroke. By contrast, the ADDTC criteria do not require the presence of focal neurologic signs and symptoms, although they state that a clear relationship between stroke and dementia onset must exist (see table 1). Therefore, we would expect to see a better agreement between the ADDTC criteria and the pre-MRI diagnosis, as the pre-MRI diagnosis was based only on abrupt onset of cognitive deficits, and less agreement between the ADDTC and the NINDS-AIREN criteria (see table 3).

Furthermore, the history of strokes does not necessarily indicate "pure" VaD, as strokes can occur in AD subjects at the onset of the neurodegenerative process (perhaps "uncovering" the syndrome) or during the course of the disease. Consequently, cross-sectional assessments of these patients may overestimate the prevalence of VaD. On the other hand, the clinical stroke can mark the beginning of a progressive cognitive process of vascular etiology, which could be difficult to distinguish from AD. Thus, regardless of study design (longitudinal or cross-sectional) and the use of strict clinical criteria, in the absence of a valid biomarker, AD cannot be completed excluded from a VaD syndrome.

The simultaneous use of the NINCDS-ADRDA criteria for AD and the ADDTC criteria for VaD allowed us to identify the full-spectrum dementia in

Table 4 *Relationship among different criteria for VaD**

	Pre-MRI diagnosis			
	Non-VaD	VaD	Mixed	κ
ADDTC criteria for VaD				
Probable	49	37	31	0.50
Possible	51	11	34	
Non-VaD	249	4	11	
NINDS-AIREN criteria for VaD				
Probable	8	25	9	0.39
Possible	1	9	0	
Non-VaD	339	18	66	
DSM-IV criteria for VaD				
VaD	10	34	58	0.44
No VaD	340	18	17	

	NINDS-AIREN criteria for VaD			
	Non-VaD	Probable	Possible	κ
ADDTC criteria for VaD				
Probable	65	42	9	0.21
Possible	94	1	1	
Non-VaD	264	0	0	

	DSM-IV criteria for VaD		
	VaD	No VaD	κ
ADDTC criteria for VaD			
Probable	57	59	0.27
Possible	3	93	
Non-VaD	1	263	
NINDS-AIREN Criteria for VaD			
Probable	36	6	0.76
Possible	9	1	
No VaD	16	407	

* Four of 480 incident cases with unclassified dementia diagnosis were not entered in the reliability study.

VaD = vascular dementia; ADDTC = State of California Alzheimer's Disease Diagnostic and Treatment Centers; NINDS-AIREN = National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders (4th ed.).

the context of vascular and nonvascular etiologies. We found that an AD component was present in the majority of the cases with dementia of vascular etiology. Indeed, only 56 (26%) of the 213 cases identified with the diagnosis of probable and possible VaD were considered to have only VaD when the two criteria were used together. Therefore, the majority of the cases with vascular disease of sufficient severity to cause cognitive deficits have also AD-like clinical features.[54]

None of the VaD criteria were able to successfully identify all the MRI-confirmed cases with VaD; depending on which criteria were used, different cases were missed. The diagnosis of VaD by the DSM-IV and NINDS-AIREN criteria appeared to identify a group of participants with more severe vascular disease, whereas the ADDTC criteria were less stringent. This latter system identified participants in the border zone between AD and VaD or those with no history of clinical strokes but with severe MRI-identified vascular disease. The majority of the participants with vascular disease had an AD-like component, either as a progressive dementia syndrome or with a cognitive pattern that was not explained by the location of the MRI-identified lesions.[56] These findings placed an important limitation on the interpretation of large population studies, especially those with clearly defined probable and possible syndromes.

The neuropsychological characteristics of the VaD cases were consistent with studies that showed that, as a group, VaD patients have global cognitive deficits.[56] Although some VaD subjects can present with more executive function deficits than those with other dementias, in this study the executive function *T* scores were not different among the non-VaD and VaD subgroups. However, the proportion of subjects with executive deficits was greater in the VaD and AD groups (86%; three VaD + AD subgroups) than in non-VaD (58%) and probable VaD (63%) groups, suggesting that AD can contribute to the executive function deficit pattern usually observed in VaD cases.

All of the dementia groups had progressive cognitive deterioration, including the cases with probable VaD. This progressive nature makes the use of the NINDS-AIREN criteria difficult because it is not possible to rule out AD. Furthermore, although the criteria require that the dementia should start within 3 months of a clinical stroke, even subjects with strong evidence of VaD can continue to progress. This could be the manifestation of a concomitant neurodegenerative disorder or an active vascular disease, which could be difficult to differentiate. A recent study showed that 21.5% of the nondemented subjects developed dementia after a stroke during a 4-year follow-up.[57] Within the first 2 years, the subjects developed AD-type dementia, whereas from year 2 to 4, they had more VaD features.

Similarly, as a group, all subjects classified with dementia had 3MSE scores that were lower than those of nondemented subjects before the onset of the dementia. This indicated that some degree of cognitive impairment preceded the onset of dementia, which could be part of a progressive neurodegenerative process, active vascular disease, or both. Pre-stroke deficits, as measured with a proxy's semistructured interview, were a strong predictor of

incident VaD,[58] and it has been reported that silent strokes were associated with incident dementia[30] and with cognitive deficits and disability.[59]

In addition to the problem posed by the overlap of etiology, the different definitions of dementia used in population studies created variability as well. For example, the DSM-IV criteria require memory deficits and impairments in at least one other cognitive domain, and the NINDS-AIREN criteria require memory deficits and cognitive impairments in two other domains (ICD-10 dementia criteria). A study that examined the agreement of six diagnostic criteria for dementia found that the proportion of diagnosed subjects with dementia varied from 3.1% (ICD-10 criteria) to 29.1% (DSM-III criteria).[60] Furthermore, both criteria require that VaD patients must have memory deficits, but it seems that whereas some VaD subjects have global cognitive deficits,[56] others can have relatively preserved memory functions.[61] Thus, subjects with lesions that do not affect memory or memory circuitry would be misclassified. It seems, therefore, that the DSM-IV and NINDS-AIREN criteria may capture the more advanced cases (i.e., three domains impaired) and risk the possibility of misclassifying cases with AD as VaD (because of the memory loss). By contrast, the ADDTC criteria do not specify how dementia is diagnosed, which gave us the flexibility to use them in combination with the NINCDS-ADRDA dementia criteria and better explore the relationship between VaD and AD.

Neuroimaging is critical for the accurate diagnosis of VaD; there is a significant discrepancy between the diagnosis made with and without MRI. However, although in some cases there is a clear relationship between the location of the stroke and the cognitive deficits, we found in the majority of the subjects the presence of multiple subcortical infarcts without a clear relationship with the cognitive syndrome. This is consistent with studies that found that VaD patients had subcortical hypometabolism compared with those with AD, although both VaD and AD patients had cortical, frontal, and temporoparietal hypometabolism,[62] and that demented subjects with subcortical ischemic lesions had cortical "microinfarct-like" lesions.[63] This complicates the notion that specific neuroimaging lesions are required for the diagnosis of VaD (i.e., NINDS-AIREN criteria) and explains the lack of agreement among radiologists when attempting to operationalize the neuroimaging component of the NINDS-AIREN criteria.[16]

The diagnosis of VaD is difficult in population studies, even when clinical longitudinal information and neuroimaging are available. These results showed that the majority of the VaD cases had AD clinical features. Therefore, the diagnosis of VaD should be done using in parallel the diagnostic criteria for VaD and for AD, assisted with neuroimaging studies.

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