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Diagnostic Criteria of Vascular Dementia in CADASIL

Sarah Benisty, MD; Karen Hernandez, MSc; Anand Viswanathan, MD, PhD; Sonia Reyes, MSc;
Annie Kurtz, MSc; Michael O'Sullivan, PhD; Marie-Germaine Bousser, MD;
Martin Dichgans, MD, PhD; Hugues Chabriat, MD, PhD

Background and Purpose—Subcortical ischemic vascular dementia (SIVD) is a major subtype of vascular dementia (VaD). Recently, the diagnostic criteria of VaD have been modified to encompass this entity. Application of these criteria in CADASIL, a genetic model of SIVD, may help to better assess their significance. The aim of this study was to compare different sets of diagnostic criteria of VaD in a population of CADASIL patients.

Methods—Different sets of diagnostic criteria of VaD (DSMIV, ICD10, standard NINDS-AIREN, modified NINDS-AIREN for SIVD) were applied to 115 CADASIL patients. Diagnosis of VaD was made through 2 steps: (1) diagnosis of dementia and (2) association of dementia to lesions of vascular origin. The percentage of patients satisfying the different sets and the concordance between these criteria was analyzed.

Results—At least 1 set of criteria was satisfied for diagnosis in 29 subjects with dementia. In this group of patients, the sensitivity of the DSM IV, ICD 10, and standard NINDS-AIREN criteria for VaD was, respectively, 79%, 72%, and 45%. In contrast, the sensitivity of the NINDS-AIREN criteria for SIVD was 90%. The incomplete sensitivity of these last criteria was related to the absence of focal signs in some patients. The neuroimaging criteria were satisfied in all patients with dementia.

Conclusions—The modified NINDS-AIREN criteria of SIVD are the most sensitive VaD criteria in CADASIL. Among these criteria, the neuroimaging criteria, although poorly specific to dementia, have a complete sensitivity. In contrast, focal signs were inconstant in CADASIL patients with dementia. (***Stroke***. 2008;39:838-844.)

Key Words: CADASIL ■ diagnostic criteria ■ leukoariosis ■ vascular dementia

Vascular dementia (VaD) is the second most common cause of dementia after Alzheimer disease.[1] In clinical research, various criteria are proposed for diagnosis of VaD, particularly in therapeutic trials. They are based on 2 major requirements: (1) clinical diagnosis of dementia and (2) determination of its vascular origin. The latter requirement is most problematic because of the frequent overlap between cerebrovascular and degenerative disorders, particularly in the elderly. Four sets of criteria have been essentially used for diagnosis of VaD: Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV),[2] Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC),[3] International Statistical Classification of Diseases, 10th revision (ICD 10),[4] and National Institute of Neurological Disorders and Stroke Association Internationale Pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria.[5] Previous analyses of these criteria showed that they were not all equivalent[6–9] In addition, because these criteria were proposed to cover the wide spectrum of VaD, none of them is able to discriminate the main subtypes of vascular dementia such as multi-infarct dementia, strategic infarct dementia, or subcortical ischemic vascular dementia (SIVD).[1]

SIVD may represent one of the most common forms of VaD. It can be caused by various types of small vessel disease that lead to lacunar infarcts and white matter lesions restricted to subcortical areas.[10] This entity was considered homogenous enough to require specific diagnostic criteria. Recently, a set of research criteria derived from the NINDS-AIREN criteria of vascular dementia was proposed.[11] These criteria rely on both clinical and radiological data. Further evaluation of their sensitivity and specificity is now needed.

In contrast to sporadic small vessel diseases frequently detected during aging in association with degenerative disorders, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a rare disease with onset occurring between age 40 and 50 years.[12] CADASIL is caused by mutations of the *Notch 3* gene on chromosome 19.[13] It is recognized as the most frequent hereditary cause of SIVD and as a model of "pure" VaD. In CADASIL, brain MRI shows widespread white matter le-

sions associated with lacunar infarcts of variable extent or number and developing from the third decade.[14] The main clinical manifestations include attacks of migraine with aura, recurrent subcortical stroke, mood disturbances, and a progressive cognitive decline leading to dementia.[12] The cognitive profile in CADASIL is characteristic of VaD and similar to that reported in sporadic SIVD.[15] Because symptoms in CADASIL develop several decades before the onset of common degenerative diseases, confounding by concomitant medical conditions is considerably reduced. Therefore, CADASIL patients with dementia can be used as a reference population to understand the limitations of diagnostic criteria currently used for VaD or recently proposed for SIVD.

In the present study, we applied different sets of diagnostic criteria for VaD in a large group of CADASIL patients to determine in this population: (1) the sensitivity of the these diagnostic criteria with respect to all demented patients detected in the cohort; (2) the sensitivity of subcriteria used for attribution of the vascular origin; and (3) the sensitivity of the modified NINDS-AIREN criteria for the diagnosis of SIVD.

Methods

Subjects

One hundred fifteen CADASIL patients followed-up in Lariboisiere Hospital (Paris, France) were included in the study. Their mean age was 53.7 ± 11.7 years, the sex ratio (male/female) was 1.01, and education level was from 3 to 7 (maximal). Diagnosis was confirmed by identification of a typical mutation in the *Notch 3* gene. Informed consent was obtained from each subject or from a close relative if the subject was too severely disabled to give written consent. The study was approved by an independent ethics committee.

Clinical Data

Clinical and demographic data were collected at the time of inclusion with detailed baseline neurological examination including the assessment of presence or absence of gait abnormalities, Parkinsonian syndrome, pyramidal signs, sensory deficit, visual field defect, dysphagia, dysarthria, or ocular palsy.

Neuropsychological Evaluation

Neuropsychological evaluation was performed in patients without severe depression after evaluation by the psychologist. Global cognitive function was assessed by the Mini-Mental State Examination[16] and Mattis Dementia Rating Scale (from 0 to 144 [best score]).[17] Memory was assessed by an explicit verbal memory test adapted from the Grober and Buschke procedure.[18,19] Executive functions were assessed by subtest of the Wechsler Adult Intelligence Scale-Revised (Similarities and Block Design),[20] the Trail Making Test B,[21] the Wisconsin Card Sorting test (revised version by Nelson),[22] and both semantic and letter verbal fluency. Except for the Wisconsin test, performances in each test were converted into z scores using normative data reported from the literature and data from healthy populations.[19] In addition to these neuropsychological tests, activities of daily living and disability attributable to cognitive impairment were assessed based on a French translation of Lawton's scale of Instrumental Activities of Daily Living (IADL).[23] The scoring of this scale was based on the interview of the patient or a close relative. Each of 8 IADL (ability to handle finances, to use the telephone, mode of transport, responsibility for own medication, etc) was assessed according to a 3- to 5-grade scale. Then the patients were given a score of 1 if they were considered nonrestricted or were given a score of 0 if they were restricted (score 0). A global score ranging from 0 to 8 was obtained.

Magnetic Resonance Imaging

MRI scans were obtained by the use of a 1.5-T system (Signa General Electric Medical Systems) as already reported.[24] The extent of white matter lesions was visually assessed on FLAIR images based on the recommendations specified in the criteria and described further. The number and location of lacunar infarcts, defined as hypointense foci of diameter >3 mm on T1 scans or on FLAIR images, were also recorded when they were not located in areas with high prevalence of widened perivascular spaces.[25,26]

Diagnosis of Vascular Dementia

In the present cohort, 4 different sets of diagnostic criteria (DSMIV, ICD-10, ADDTC, NINDS-AIREN) were considered for the diagnosis of VaD. The diagnosis was performed using a 2-step procedure: (1) diagnosis of dementia and (2) association of the dementia to lesions of vascular origin.

Diagnosis of Dementia

For the DSM IV, ICD-10, and standard NINDS-AIREN criteria for VaD, although slight differences in its formulation, the diagnosis of dementia in each patient was made by 1 of 2 expert neurologists, after discussion and agreement with the neuro-psychologist who performed the cognitive testing, according to a unique definition based on the DSM IV criteria for dementia.[2]

For the modified NINDS-AIREN research criteria for SIVD,[11] the diagnosis of dementia was made separately based on available neuropsychological data and using a criteria-based algorithm. This definition of dementia includes a memory deficit that can be mild or severe and characterized by impaired recall, relative intact recognition, less severe forgetting, and benefit from cues, and a dysexecutive syndrome. This cognitive deficit should interfere with complex (executive) activities of daily living and not be attributable to physical effects of the cerebrovascular disease alone. Thus, in the present study, a patient was considered to be demented when presenting with a cognitive deficit characterized by reduced performances (z scores ≤ 1.65) for the total free recall (memory impairment) of the Grober and Buschke procedure and for at least 2 of the following tests of executive function: Similarities, Cubes, Trail Making Test B, verbal fluency, or <6 criteria found with the Wisconsin test. Additionally, these cognitive alterations had to be associated with at least 2 impaired instrumental activities of daily living as reflected by IADL score ≤ 6 (IADL items were preferred to ADL items because they are altered earlier in the course of dementia[27]).

Attribution of Dementia to Lesions of Vascular Origin According to DSMIV, ICD 10, ADDTC, NINDS-AIREN, and Modified NINDS-AIREN Diagnostic Criteria of VaD

The different set of criteria considered in this study require various neuroimaging evidence of cerebrovascular disease, focal neurological signs, or history of stroke with a temporal relationship with dementia. DSM IV criteria for VaD require only neuroimaging evidence of cerebrovascular disease judged to be etiologically related to cognitive alterations.[2]

ICD10 criteria for VaD require neuroimaging evidence of cerebrovascular disease "reasonably judged to be etiologically related to dementia" and the presence of focal neurological findings such as unilateral spastic weakness of the limb, unilaterally increased tendon reflexes, extensor plantar response, or pseudobulbar palsy.[4]

The ADDTC criteria for possible VaD include clinical and neuroimaging evidence of Binswanger disease, but without any specification for this "evidence."[28] To avoid redundancy with other sets of criteria in the absence of clear definition of "Binswanger's disease," we chose not to include these criteria in the present analysis.

According to the standard NINDS-AIREN criteria,[5] the diagnosis of probable VaD in patients with dementia requires the following conditions: (1) presence of focal signs at neurological examination

Table 1. Diagnosis of Dementia According to the DSMIV Criteria and to the Definition of the Modified NINDS-AIREN Criteria for SIVD in 115 CADASIL Patients

	n (%)
DSM IV dementia criteria	23 (20)
Cognitive syndrome described in the modified NINDS-AIREN criteria for SIVD	28 (24)
z score ≤1.65 for total free recall of the Grober procedure	38 (33)
z score ≤1.65 in ≥2 tests for dysexecutive syndrome	62 (54)
IADL ≤6	34 (29)
Concordance (% of overlapping cases with and without dementia)	108/115 (94)

The % was obtained on the whole population.

such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, or dysarthria; (2) evidence of a temporal relationship between the onset of dementia and stroke or an abrupt deterioration or fluctuating/stepwise course; and (3) presence on brain imaging of extensive periventricular white matter lesions involving at least 25% of the total white matter or multiple basal ganglia and white matter lacunes.

Finally, the NINDS-AIREN modified research criteria for subcortical ischemic vascular dementia[11] require clinical evidence of cerebrovascular disease, ie, focal signs such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, dysarthria, gait disorders, extrapyramidal signs (others signs such as early urinary symptoms, behavioral symptoms, dysphagia were considered to "support" the diagnosis; and brain imaging evidence of cerebrovascular disease. Two types of cases were distinguished by visual assessment on MRI: (1) predominantly white matter cases characterized by extending periventricular and deep white matter lesions: extending caps or irregular halo (>10 mm broad) and diffuse confluent hyperintensities (>25 mm) and at least 1 lacunar infarct in the deep gray matter; and (2) predominant "lacunar cases" in which multiple lacunes ≥5 in the deep gray matter were associated with at least moderate white matter lesions.

Statistical Procedure

The different percentages of patients satisfying the various sets of diagnostic criteria for dementia as well as for vascular dementia were estimated in the whole cohort. The sample of patients satisfying at least one set of criteria for dementia was considered as the reference population for analysis of sensitivity. This population, the largest sample with demented subjects (to reduce bias related to the definition of dementia), was chosen to compare different sets of diagnostic criteria.

The results obtained after using the diagnostic criteria for dementia are presented first with the main clinical characteristics of the demented population. Thereafter, the MRI and clinical features of demented patients are detailed according to the different sets of diagnostic criteria. The distribution of vascular dementia and concordance between these sets of criteria (for each pair of sets, percentage of patients satisfying both criteria) are then reported.

Results

Diagnosis of Dementia

Among the 115 patients included in the study, 23 (20%) subjects fulfilled the DSM IV criteria for dementia and 28 (24%) patients satisfied the conditions of the modified NINDS-AIREN criteria of dementia for SIVD (Table 1). Note that 34 patients who had significant impairment in executive functions did not have dementia (29% of the whole cohort). There were 22 overlapping cases between these sets of criteria and a total of 29 patients who satisfied either the

Table 2. Average Scores of MMSE, MDRS, and IADL (mean value±SD, range) in Patients Satisfying Both DSMIV and Modified NINDS-AIREN Criteria of Dementia and in Patients Only Satisfying the Modified NINDS-AIREN Criteria of Dementia

	DSMIV and Modified NINDS-AIREN Criteria of Dementia (n=22)*	Only Modified NINDS-AIREN Criteria of Dementia (n=6)
MMSE	16.4±5.7	26.6±3.4
MDRS	84.9±27.3	119±9.5
IADL	0.87±1.63	4.3±1.2

*MMSE scores and MDRS were obtained in only 15 of the patients with dementia. Eight subjects were too severely disabled to complete the tasks (27% of all patients with dementia).

first set of criteria or the second (concordance between the 2 definitions on the whole cohort of 94%). This group of 29 patients served as the reference group for sensitivity analysis. Their mean age was 62±8.8 years (50.8±11.3 years in the group of patients without dementia), and sex ratio (M/F) was 2.2 (0.8 in the group of patients without dementia). Only a single patient was considered to be demented according to DSM IV criteria but did not fulfill the algorithm derived from the modified NINDS-AIREN criteria of dementia for SIVD (this case did not show any significant impairment of total free recall). Six patients without dementia according to DSM IV criteria fulfilled the conditions required in the modified NINDS-AIREN criteria for SIVD ("nonoverlapping cases"). Average scores of these patients for global cognitive scales and IADL are presented in Table 2. Among the 22 overlapping cases, 15 (70%) had a severe disability (IADL ≤1), whereas the IADL was ≥4 in only 2 patients (8%). In contrast, for 4 out of the 6 "nonoverlapping cases," the IADL was ≥4 and none had IADL ≤1.

Attribution of Dementia to Lesions of Vascular Origin According to DSMIV, ICD 10, NINDS-AIREN, and Modified NINDS-AIREN Diagnostic Criteria of VaD

In our cohort, all 29 patients who satisfied at least 1 set of diagnostic criteria for dementia presented on MRI with extensive white matter lesions of vascular origin. Therefore, all CADASIL patients fulfilling the DSM IV criteria for dementia (n=23) were considered to satisfy the DSMIV criteria of VaD. Among them, 21 patients also had a pyramidal syndrome or pseudobulbar palsy and thus satisfied the ICD10 criteria. Finally, only 13 of them had a clinical history of stroke associated with focal signs and consequently satisfied the standard NINDS-AIREN criteria of probable VaD (Table 3). Thus, in this group of 23 patients with dementia, the sensitivity of the DSM IV , ICD 10, and standard NINDS-AIREN criteria for VaD was, respectively, 100%, 91%, and 56%.

All 28 patients satisfying the modified NINDS-AIREN criteria of dementia for SIVD presented with extending caps and confluent hyperintensities in the white matter and at least 1 lacunar infarct in the deep gray matter (range of total number of lacunes from 2 to 39). Thus, all fulfilled the imaging criteria of the modified NINDS-AIREN definition of SIVD and could be considered as "predominantly white

Table 3. Diagnosis of VaD According to Different Sets of Criteria in 115 CADASIL Patients

VaD Criteria	DSM IV Criteria	ICD-10 Criteria	Standard NINDS-AIREN Criteria	Modified SIVD NINDS-AIREN Criteria
Definition of dementia	Cognitive deterioration with memory impairment, IADL impaired			Memory deficit,* dysexecutive syndrome,* IADL impaired*
Attribution of dementia to lesions of vascular origin	Neuroimaging evidence of CVD (NS)		Neuroimaging evidence of CVD such as extensive WML or multiple basal ganglia and WM lacunar infarcts and history of stroke and temporal relationship	Extensive WML and ≥I lacune in deep gray matter or multiple deep gray matter lacunar infarcts
	±Focal Signs (NS)	Focal Signs (pyramidal signs)	Focal Signs†	
N of patients	23	21	13	26
Total with dementia, %	79	72	45	90
Total patients, %	20	18	11	23

CVD indicates cerebrovascular disease; NS, not specified; WML, white matter lesions.

*z score ≤1.65 for total free recall of the Grober procedure.

z score ≤1.65 in ≥2 tests for dysexecutive syndrome.

IADL ≤6.

†Focal signs among the following: hemiparesis, pyramidal signs, sensory deficit, dysarthria, gait disorders, and extrapyramidal signs.

matter" cases. However, the complete modified NINDS-AIREN criteria for SIVD were fulfilled by only 26 out of the 28 patients because 2 patients did not show any focal signs at neurological examination. Thus, in this group of 28 patients with dementia, the sensitivity of the modified NINDS-AIREN criteria for SIVD was 93%. In addition, 29 out of 86 (33%) CADASIL patients without dementia also fulfilled the imaging diagnostic criteria of SIVD in the present cohort.

If the whole group of patients with dementia was considered as the reference group (n=29), the overall sensitivity of the DSM IV, ICD 10, standard NINDS-AIREN criteria for VaD, and for modified NINDS-AIREN criteria for SIVD was, respectively, 79%, 72%, 45%, and 90%.

The detailed results at the individual level after the application of the different sets of diagnostic criteria are presented in Figure. The concordance between the different sets of criteria was incomplete and varied between 86% and 98.2% as detailed in Table 4. This incomplete concordance is illustrated at the individual level by Figure. Finally, the associated clinical features in demented patients according to the modified NINDS-AIREN criteria are detailed in Table 5. Gait disturbances and pyramidal signs were detected in 92% of this population, whereas focal deficits such as sensory or visual field defects were detected in <12%.

Discussion

In this study, we applied different sets of diagnostic criteria of VaD to a cohort of 115 CADASIL patients who were at various stages of the disease. Our study shows that, in a large population of patients with subcortical brain lesions of vascular origin, dementia as defined by the modified criteria for SIVD is observed in a larger population than dementia as defined by the DSMIV criteria, mainly developed for the diagnosis of Alzheimer disease. In addition, in the demented patients satisfying both sets of criteria, ≈70% of subjects had a severe disability. In contrast, none of those exclusively diagnosed by the modified criteria for SIVD ("nonoverlap-

ping cases") had a similar status and two-thirds had IADL ≥4. Such results suggest that the subcriteria for dementia derived from the modified NINDS-AIREN criteria for SIVD are more sensitive than the DSMIV criteria to early stages of dementia occurring in a small vessel disease of the brain. These data also emphasize the importance of executive dysfunction in the clinical expression of SIVD, and further confirm that the traditional definition of dementia focused on memory impairment is actually too "Alzheimerized"[30] for dementia caused by small vessel diseases.[31] In addition, in the present study, the use of both sets of criteria of dementia circumscribed less than one-third of the cohort patients. Most of them were at an advanced stage of the disease and 27% patients were even unable to complete the cognitive evaluation because they were too severely impaired. Of note, about one third of subjects in the cohort were outside the demented group but had significant executive alterations in the absence of severe disability. This group of patients may fall within the recently individualized category designated as "vascular mild cognitive impairment."[31,32]

The use of a cut-off value for global cognitive scales is a frequent alternative approach to the diagnosis of dementia, particularly in large-scale studies. Herein, the data showed that the mean Mini-Mental State Examination score of demented patients at the early stage of dementia (nonoverlapping cases satisfying only the modified NINDS-AIREN criteria) is 26.6, beyond the usually accepted cut-off score of 24 used for dementia in degenerative disorders.[33] Conversely, the mean Mattis Dementia Rating Scale score of these subjects was below the usual cut-off score of 127 found in the literature.[34] The underestimation of executive dysfunction in the Mini-Mental State Examination compared with the Mattis Dementia Rating Scale may explain this discrepancy. These results support that the Mattis Dementia Rating Scale, used as a global scale, should be preferred to delineate the group of subjects with dementia in CADASIL and, probably, in other small vessel disorders.
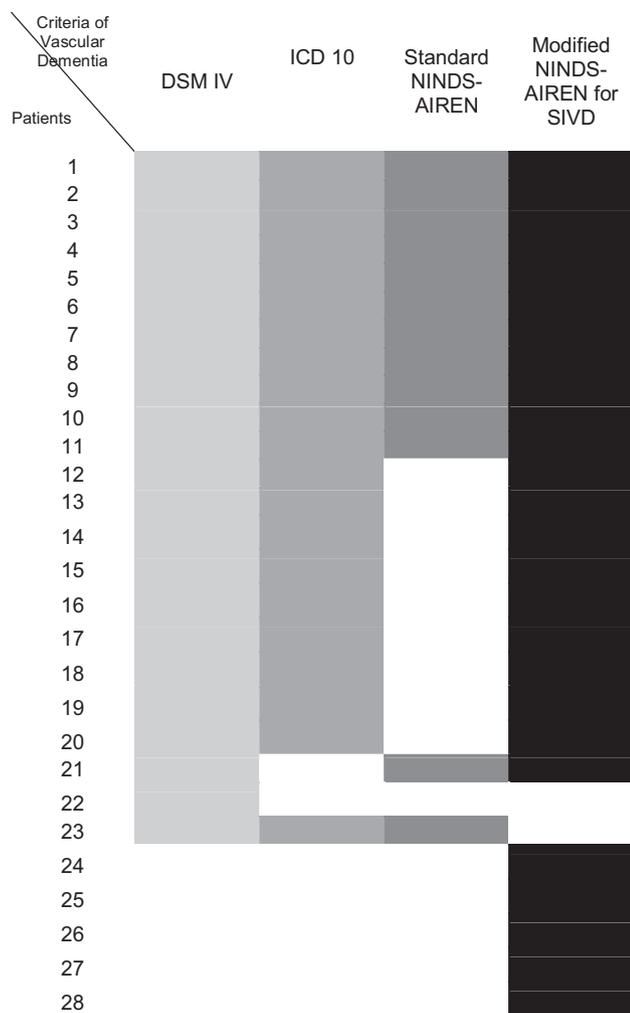
Figure. Distribution of vascular dementia according to the different set of criteria. *Note that 1 patient satisfying only the modified NINDS-AIREN criteria for dementia but not the complete criteria for SIVD is not included here.

The application of different sets of VaD diagnostic criteria in the CADASIL cohort resulted in incompletely overlapping groups as previously reported in different populations.[6–9] The DSM IV and ICD-10 criteria for VaD, as well as the standard NINDS-AIREN criteria, were found to be of variable sensitivity in demented patients with CADASIL. The comparison of the Standard NINDS-AIREN criteria for VaD and the modified research ones for SIVD showed that the latter criteria significantly increase the diagnostic sensitivity, which

Table 4. Concordance Between Criteria for the Diagnosis of Vascular Dementia in 115 CADASIL Patients

Applied Criteria	Concordance %
DSM IV/ICD 10	98.2
DSM IV/standard NINDS-AIREN for probable VaD	91.3
DSM IV/modified NINDS-AIREN for SIVD	95.6
ICD 10/standard NINDS-AIREN for probable VaD	93
ICD 10/modified NINDS-AIREN for SIVD	93
Standard NINDS-AIREN for probable VaD/ modified NINDS-AIREN for SIVD	86

Table 5. Clinical Features of Patients Satisfying the Modified NINDS-AIREN Criteria for SIVD (n=26)

	Modified NINDS-AIREN Criteria for SIVD, n=26 (%)
Pyramidal signs	24 (92)
Gait disorders	24 (92)
Urinary disorders	21 (80)
Clinical history of ≥1 stroke	15 (57)
Dysarthria	14 (54)
Swallowing problems	10 (38)
Extrapyramidal symptoms	5 (19)
Sensory deficit	3 (11)
Visual field defect	2 (7)

remains, however, <100%. The positive "history of stroke" when used as a criterion was responsible for the poor sensitivity of the NINDS-AIREN definition of probable VaD in our population. In contrast to some subtypes of VaD such as multi-infarct VaD or poststroke dementia,[1] for which this criterion is a prerequisite, its use in CADASIL patients appears less valid because the cognitive decline may be progressive and independent of stroke events.[35] In addition, our data also show that although the presence of focal signs of stroke was present in most demented subjects, 2 cases did not fulfill the modified NINDS-AIREN criteria for SIVD because of the lack of any focal deficit. These results are in line with those of Pohjaswaara et al[36] who previously reported that patients with sporadic SIVD can present without any focal signs of stroke. This suggests that this criterion should be considered as a supportive symptom rather than as a prerequisite in the definition of SIVD. Interestingly, we also observed that the presence of gait disorders and pyramidal symptoms was much more frequent than sensory deficits or visual field defects in CADASIL patients, which suggests that all focal symptoms of stroke are not of equivalent sensitivity for defining SIVD.

Imaging criteria are also considered for diagnosis of VaD. In our cohort, all patients with dementia showed extensive white matter lesions and at least 1 lacunar infarct in the deep gray matter as required in the "Binswanger type" definition of SIVD. Extensive white matter lesions on T2 and FLAIR are significantly correlated with clinical severity or executive performances in small vessel diseases.[37] However, they may be insufficiently discriminating for the diagnosis of dementia. In a population of poststroke elderly patients, Ballard et al[29] observed that the amount of white matter lesions, and the cut-off built into the standard NINDS-AIREN imaging criteria, did not discriminate between patients with and without dementia. In the present cohort, both extensive white matter lesions and the presence of a lacunar infarct were detected in one-third of patients without dementia, which further supports that the NINDS-AIREN imaging criteria of SIVD have poor specificity in this subtype of dementia. The total amount of lacunar lesions and also the degree of atrophy were recently found to be the most potent imaging predictors of cognitive impairment in CADASIL.[24,25,38] Further studies may help to determine whether a detailed analysis of location

of small deep infarcts, the exact measurement of their load, or the estimation of cerebral atrophy can further improve the diagnosis of SIVD.[39]

The main limitation of this study concerns the small number of patients with dementia recruited in the cohort. However, this is compensated by the strong homogeneity of the group of patients having an identical vascular disease. In the absence of consensus in the definition of dementia, the calculation of sensitivity required the choice of a reference population for patients with dementia (the largest sample of demented subjects in the present study). Another limitation of this study is that specificity of SIVD criteria could not be determined herein because we evaluated diagnostic criteria in a population with all patients having a vascular disorder. Other populations with dementia but without vascular disorders are needed for this purpose.

Conclusion

In conclusion, our results demonstrate that the modified NINDS-AIREN criteria proposed for SIVD actually improve the diagnosis of VaD related to small vessel diseases and suggest that some refinements may further improve its sensitivity. The present data suggest that some clinical features such as a positive history of stroke or presence of focal signs should not be mandatory for diagnosis of SIVD. In contrast, whether new imaging features such as the load of lacunar infarctions, the location of such lesions, or estimation of the degree of atrophy may improve the diagnosis of SIVD will need further investigation.

Disclosures

None.

References

1. O'Brien JT, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L, Bowler JV, Ballard C, DeCarli C, Gorelick PB, Rockwood K, Burns A, Gauthier S, DeKosky ST. Vascular cognitive impairment. *Lancet Neurol*. 2003;2:89–98.
2. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. Washington, DC: American Psychiatric Press; 1994.
3. Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the state of California Alzheimer's disease diagnostic and treatment centers. *Neurology*. 1992;42:473–480.
4. World Health Organization. *TheICD-10 classification of mental and behavioral disorders: Diagnostic criteria for research*. Geneva: WHO; 1993.
5. Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo JM, Brun A, Hofman A, et al. Vascular dementia: Diagnostic criteria for research studies. Report of the ninds-airen international workshop. *Neurology*. 1993;43:250–260.
6. Wetterling T, Kanitz RD, Borgis KJ. Comparison of different diagnostic criteria for vascular dementia (ADDTC, DSM-IV, ICD-10, NINDS-AIREN). *Stroke*. 1996;27:30–36.
7. Pohjasvaara T, Mantyla R, Ylikoski R, Kaste M, Erkinjuntti T. Comparison of different clinical criteria (DSM-III, ADDTC, ICD-10, NINDS-AIREN, DSM-IV) for the diagnosis of vascular dementia. National institute of neurological disorders and stroke-association internationale pour la recherche et l'enseignement en neurosciences. *Stroke*. 2000;31:2952–2957.
8. Gold G, Bouras C, Canuto A, Bergallo MF, Herrmann FR, Hof PR, Mayor PA, Michel JP, Giannakopoulos P. Clinicopathological validation study of four sets of clinical criteria for vascular dementia. *Am J Psych*. 2002;159:82–87.
9. Lopez OL, Kuller LH, Becker JT, Jagust WJ, DeKosky ST, Fitzpatrick A, Breitner J, Lyketsos C, Kawas C, Carlson M. Classification of vascular dementia in the cardiovascular health study cognition study. *Neurology*. 2005;64:1539–1547.
10. Roman GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. *Lancet Neurol*. 2002;1:426–436.
11. Erkinjuntti T, Inzitari D, Pantoni L, Wallin A, Scheltens P, Rockwood K, Roman GC, Chui H, Desmond DW. Research criteria for subcortical vascular dementia in clinical trials. *J Neural Transm Suppl*. 2000;59:23–30.
12. Chabriat H, Vahedi K, Iba-Zizen MT, Joutel A, Nibbio A, Nagy TG, Krebs MO, Julien J, Dubois B, Ducrocq X, et al. Clinical spectrum of CADASIL: A study of 7 families. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Lancet*. 1995;346:934–939.
13. Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, Alamowitch S, Domenga V, Cecillion M, Marechal E, Maciazek J, Vayssiere C, Cruaud C, Cabanis EA, Ruchoux MM, Weissenbach J, Bach JF, Bousser MG, Tournier-Lasserve E. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature*. 1996;383:707–710.
14. Chabriat H, Levy C, Taillia H, Iba-Zizen MT, Vahedi K, Joutel A, Tournier-Lasserve E, Bousser MG. Patterns of MRI lesions in CADASIL. *Neurology*. 1998;51:452–457.
15. Charlton RA, Morris RG, Nitkunan A, Markus HS. The cognitive profiles of CADASIL and sporadic small vessel disease. *Neurology*. 2006;66:1523–1526.
16. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189–198.
17. Mattis S. Mental status examination for organic mental syndrome in elderly patients. In: Bellak LKT, ed. *Geriatric psychiatry: A handbook for psychiatrists and primary care physicians*. New York: Grune&Stratton; 1976:77–121.
18. Van der Linden MWC, Bruyer R, Ansay C, Seron X. Educational level and cued recall performance in older and young adults. *Psychologica Belgica*. 1993;33:37–47.
19. Buffon F, Porcher R, Hernandez K, Kurtz A, Pointeau S, Vahedi K, Bousser MG, Chabriat H. Cognitive profile in CADASIL. *J Neurol Neurosurg Psych*. 2006;77:175–180.
20. Wechsler D. Wechsler adult intelligence scale revised (WAIS-R). 1981. les Editions du Centre de Psychologie Appliqué, 1991.
21. Reitan RM. The relation of the trail making test to organic brain damage. *J Consult Psychol*. 1955;19:393–394.
22. Nelson HE. A modified card sorting test sensitive to frontal lobe defects. *Cortex*. 1976;12:313–324.
23. Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist*. 1969;9:179–186.
24. Jouvent E, Viswanathan A, Mangin JF, O'Sullivan M, Guichard JP, Gschwendtner A, Cumurciuc R, Buffon F, Peters N, Pachai C, Bousser MG, Dichgans M, Chabriat H. Brain atrophy is related to lacunar lesions and tissue microstructural changes in CADASIL. *Stroke*. 2007;38:1786–1790.
25. Viswanathan A, Gschwendtner A, Guichard JP, Buffon F, Cumurciuc R, O'Sullivan M, Holtmannspotter M, Pachai C, Bousser MG, Dichgans M, Chabriat H. Lacunar lesions are independently associated with disability and cognitive impairment in CADASIL. *Neurology*. 2007;69:172–179.
26. Viswanathan A, Guichard JP, Gschwendtner A, Buffon F, Cumurcuic R, Boutron C, Vicaut E, Holtmannspotter M, Pachai C, Bousser MG, Dichgans M, Chabriat H. Blood pressure and haemoglobin a1c are associated with microhaemorrhage in CADASIL: A two-centre cohort study. *Brain*. 2006;129:2375–2383.
27. Barberger-Gateau P, Commenges D, Gagnon M, Letenneur L, Sauvel C, Dartigues JF. Instrumental activities of daily living as a screening tool for cognitive impairment and dementia in elderly community dwellers. *J Am Geriatr Soc*. 1992;40:1129–1134.
28. Chui HC, Mack W, Jackson JE, Mungas D, Reed BR, Tinklenberg J, Chang FL, Skinner K, Tasaki C, Jagust WJ. Clinical criteria for the

diagnosis of vascular dementia: A multicenter study of comparability and interrater reliability. *Arch Neurol*. 2000;57:191–196.

29. Ballard CG, Burton EJ, Barber R, Stephens S, Kenny RA, Kalaria RN, O'Brien JT. NINDS AIREN neuroimaging criteria do not distinguish stroke patients with and without dementia. *Neurology*. 2004;63: 983–988.

30. Sachdev P. Vascular cognitive disorder. *Int J Geriatr Psych*. 1999;14: 402–403.

31. Roman GC, Sachdev P, Royall DR, Bullock RA, Orgogozo JM, Lopez-Pousa S, Arizaga R, Wallin A. Vascular cognitive disorder: A new diagnostic category updating vascular cognitive impairment and vascular dementia. *J Neurol Sci*. 2004;226:81–87.

32. Bowler JV. Vascular cognitive impairment. *J Neurol Neurosurg Psych*. 2005;76(Suppl 5):v35–v44.

33. Madureira S, Verdelho A, Ferro J, Basile AM, Chabriat H, Erkinjuntti T, Fazekas F, Hennerici M, O'Brien J, Pantoni L, Salvadori E, Scheltens P, Visser MC, Wahlund LO, Waldemar G, Wallin A, Inzitari D. Development of a neuropsychological battery for the leukoaraiosis and disability in the elderly study (LADIS): Experience and baseline data. *Neuroepidemiology*. 2006;27:101–116.

34. Lucas JA, Ivnik RJ, Smith GE, Bohac DL, Tangalos EG, Kokmen E, Graff-Radford NR, Petersen RC. Normative data for the Mattis dementia rating scale. *J Clin Exp Neuropsychol*. 1998;20:536–547.

35. Desmond DW, Moroney JT, Lynch T, Chan S, Chin SS, Mohr JP. The natural history of CADASIL: A pooled analysis of previously published cases. *Stroke*. 1999;30:1230–1233.

36. Pohjasvaara T, Mantyla R, Ylikoski R, Kaste M, Erkinjuntti T. Clinical features of MRI-defined subcortical vascular disease. *Alzheimer Dis Assoc Disord*. 2003;17:236–242.

37. Sachdev PS, Brodaty H, Valenzuela MJ, Lorentz L, Looi JC, Wen W, Zagami AS. The neuropsychological profile of vascular cognitive impairment in stroke and TIA patients. *Neurology*. 2004;62:912–919.

38. Peters N, Holtmannspotter M, Opherk C, Gschwendtner A, Herzog J, Samann P, Dichgans M. Brain volume changes in CADASIL: A serial MRI study in pure subcortical ischemic vascular disease. *Neurology*. 2006;66:1517–1522.

39. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med*. 2003;348:1215–1222.