Diagnostic Criteria of Vascular Dementia in CADASIL

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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 (DSM IV, ICD 10, 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 equivalent6–9 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 homogeneous 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. The main clinical manifestations include attacks of migraine with aura, recurrent subcortical stroke, mood disturbances, and a progressive cognitive decline leading to dementia. The cognitive profile in CADASIL is characteristic of VaD and similar to that reported in sporadic SIVD. 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 Lariboisiére 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 and Mattis Dementia Rating Scale (from 0 to 144 [best score]). Memory was assessed by an explicit verbal memory test adapted from the Grober and Buschke procedure. Executive functions were assessed by subtest of the Wechsler Adult Intelligence Scale-Revised (Similarities and Block Design), the Trail Making Test B, the Wisconsin Card Sorting test (revised version by Nelson), 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. 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). 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. 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.

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.

For the modified NINDS-AIREN research criteria for SIVD, 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 the IADL score ≥6 (IADL items were preferred to ADL items because they are altered earlier in the course of dementia).

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.

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.

The ADDTC criteria for possible VaD include clinical and neuroimaging evidence of Binswanger disease, but without any specification for this “evidence.” 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, the diagnosis of probable VaD in patients with dementia requires the following conditions: (1) presence of focal signs at neurological examination...
Concordance (% of overlapping cases with and without dementia)

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

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 requires clinical evidence of cerebrovascular disease, ie, focal signs such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, dysarthria, gait disorders, extrapyramidal signs (other 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 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, the % was obtained on the whole population).

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

<table>
<thead>
<tr>
<th>VaD Criteria</th>
<th>DSM IV Criteria</th>
<th>ICD-10 Criteria</th>
<th>Standard NINDS-AIREN Criteria</th>
<th>Modified SIVD NINDS-AIREN Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition of dementia</td>
<td>Cognitive deterioration with memory impairment, IADL impaired</td>
<td>Neuroimaging evidence of CVD (NS)</td>
<td>Neuroimaging evidence of CVD such as extensive WML or multiple basal ganglia and WM lacunar infarcts and history of stroke and temporal relationship</td>
<td>Memory deficit,* dysexecutive syndrome,* IADL impaired*</td>
</tr>
<tr>
<td>Attribution of dementia to lesions of vascular origin</td>
<td>Neuroimaging evidence of CVD (NS)</td>
<td>Neuroimaging evidence of CVD such as extensive WML or multiple basal ganglia and WM lacunar infarcts and history of stroke and temporal relationship</td>
<td>Extensive WML and lacune in deep gray matter or multiple deep gray matter lacunar infarcts</td>
<td></td>
</tr>
</tbody>
</table>

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.

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

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 DSM IV 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 (“nonoverlapping 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 DSM IV 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” for dementia caused by small vessel diseases. 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.”

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. Conversely, the mean Mattis Dementia Rating Scale score of these subjects was below the usual cut-off score of 127 found in the literature. 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.
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 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 definition of probable VaD because of the lack of any focal deficit. These results are in line with those of Pohjaswaara et al36 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 al29 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 in the deep gray matter were required for the diagnosis of SIVD.

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

<table>
<thead>
<tr>
<th>Applied Criteria</th>
<th>Concordance %</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM IV/ICD 10</td>
<td>98.2</td>
</tr>
<tr>
<td>DSM IV/standard NINDS-AIREN for probable VaD</td>
<td>91.3</td>
</tr>
<tr>
<td>DSM IV/modified NINDS-AIREN for SIVD</td>
<td>95.6</td>
</tr>
<tr>
<td>ICD 10/standard NINDS-AIREN for probable VaD</td>
<td>93</td>
</tr>
<tr>
<td>ICD 10/modified NINDS-AIREN for SIVD</td>
<td>93</td>
</tr>
<tr>
<td>Standard NINDS-AIREN for probable VaD/modified NINDS-AIREN for SIVD</td>
<td>86</td>
</tr>
</tbody>
</table>
of small deep infarcts, the exact measurement of their load, or the estimation of cerebral atrophy may further improve the diagnosis of SIVD.\textsuperscript{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.

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Disclosures

None.

References


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