

Comparability of the Clinical Diagnostic Criteria for Vascular Dementia: A Critical Review. Part I

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This review is the first of a two-part series focusing on the comparability of eight clinical criteria used for the diagnosis of vascular dementia: the Hachinski Ischemic Scale; the Ischemic Scale of Rosen; the criteria proposed by the Diagnostic and Statistical Manual of Mental Disorder—Third Edition (DSM-III), DSM-III-R, DSM-IV; International Classification of Diseases, 10th Revision (ICD-10); State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC); and the National Institute of Neurological Disorders and Stroke—Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN). The authors discuss the critical issues related to the definition of the cognitive syndromes as well as the vascular causes and associated heterogeneity of symptomatology across these criteria.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2008; 20:150–161)

Vascular dementia is the second leading cause of dementia after Alzheimer's disease¹ and remains a diagnostic challenge in clinical settings all over the world.² As a clinical syndrome, vascular dementia relates to different vascular mechanisms and changes in the brain and has different causes and clinical manifestations.³ Vascular dementia is not limited to multi-infarct dementia, as was initially proposed by Hachinski in 1974.⁴ The pathophysiology of vascular dementia indeed incorporates interactions between vascular etiologies such as cerebrovascular diseases and vascular risk factors; changes in the brain such as infarcts, white matter lesions, and atrophy; host factors such as age, education, and sex; and cognition factors such as impairments in executive functions and psychomotor speed.^{5–7} Therefore, critical issues related to the classification and diagnosis of vascular dementia include the definition of the cognitive syndrome (i.e., the type, extent and combination of cognitive impairments) as well as the vascular causes and brain changes.

There is now an increasing effort in clinical neurosci-

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ences to detect prodromal symptoms of various dementia illnesses,⁸ including that of vascular dementia.^{9,10} Early diagnosis is certainly of great importance because nootropic drugs are now available for treatment of mild to moderate dementia.¹¹ Two well-recognized clinical criteria sets for the diagnosis of Alzheimer's disease—the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)¹² and the criteria of the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition—are currently used and reach sensitivity rates of nearly 90%.^{13–15} This relative diagnostic success with Alzheimer's disease has allowed the development of criteria for the diagnosis of mild cognitive impairment of the amnesic type, which is believed to be a prodromal phase of Alzheimer's disease.^{8,16} On the other hand, at least eight different clinical diagnostic criteria sets for vascular dementia or multi-infarct dementia have been used in clinical and research settings: the original Hachinski Ischemic Scale¹⁷ and its modified version, the Ischemic Scale of Rosen;¹⁸ the criteria proposed by the DSM-III, DSM-III-R, and DSM-IV; the International Classification of Diseases, 10th Revision (ICD-10); the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC);¹⁹ and by the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN).²⁰ Before developing criteria for the preclinical phase of vascular dementia, the validity of the current clinical diagnostic criteria for vascular dementia should be assessed and ascertained. Therefore the current qualitative review aims at describing and comparing the above-mentioned criteria according to their respective definition of the cognitive syndrome and their description of the vascular causes necessary for the diagnosis of vascular dementia. The ultimate goal is thus to present critical issues related to the diagnosis of vascular dementia. The present article is the first part of a systematic review containing two parts. Part 2²¹ examines the differential sensitivity and specificity rates of the eight diagnostic criteria and makes suggestions to improve the current criteria for vascular dementia.

Description of the Different Clinical Criteria and Their Deficit Requirements

The different clinical criteria used to diagnose vascular dementia or multi-infarct dementia are detailed and

compared in Table 1 and Table 2. Table 1 presents the cognitive syndrome, vascular causes and their relationships for each set of criteria for vascular dementia, whereas Table 2 presents the additional features mentioned in these criteria.

The Ischemic Scales The Hachinski Ischemic Scale¹⁷ and the Ischemic Scale of Rosen (IS-R)¹⁸ assign a 1 or 2 point value to each medical feature, and the final summation of these points results in an Ischemic Score. In patients with dementia, a Hachinski Ischemic Scale score ≤ 4 (IS-R ≤ 2) suggests a diagnosis of Alzheimer's disease, whereas a Hachinski Ischemic Scale score ≥ 7 (IS-R = 4–10) suggests a diagnosis of multi-infarct dementia. An intermediate Hachinski Ischemic Scale score of 5–6 suggests a diagnosis of mixed dementia. However, these scales do not include any definition of the cognitive syndrome associated with the diagnosis of multi-infarct dementia. They also do not mention any specific location for the vascular lesions required in order to meet the criteria of multi-infarct dementia.

The DSM Criteria The different sets of DSM criteria—DSM-III, DSM-III-R, and DSM-IV—require memory impairment and other cognitive deficits in various cognitive domains to reach a diagnosis of vascular dementia. These deficits must be “sufficiently severe to cause impairment in occupational or social functioning” and represent a “decline from a previous higher level of functioning.” The principal difference between the various DSM sets of criteria concerns the requirements for memory impairment. The DSM-III and DSM-IV criteria require alterations *either* in anterograde or retrograde memory, whereas the DSM-III-R criteria require impairments in *both* systems of memory. Another difference between these three sets of criteria concerns their requirement for vascular disease. The DSM-III and DSM-III-R require focal neurological signs/symptoms *and* evidence from history or physical examination of significant cerebrovascular diseases judged to be etiologically related to the disturbances. The DSM-IV requires either focal neurological signs/symptoms *or* significant cerebrovascular diseases, such as multiple infarcts in the cortex and subcortical white matter, that are judged to be etiologically related to the disturbances. Moreover, the DSM-III and DSM-III-R criteria require an abrupt onset and a stepwise deteriorating course with “patchy” distribution of cognitive deficits, although according to the DSM-IV, the onset can also be insidious and followed

TABLE 1. Comparison of the Cognitive Syndrome and Vascular Causes Required by the Diagnostic Criteria for Vascular Dementia

NOSOLOGY	HIS MID	IS-R MID	DSM- III MID	DSM- III-R MID	DSM-IV VaD	ICD-10 VaD	ADDTC IVD	NINDS- AIREN VaD
Criteria for Dementia								
Memory impairment	-	-	+	+	+	+	any deficits in ≥ 2 cognitive domains	+
Anterograde amnesia								
Retrograde amnesia	-	-	or +	and +	or +	or +		or +
Other cognitive impairments (number of domains)	-	-	≥ 1	≥ 1	≥ 1	≥ 2		≥ 2
Cognitive decline	-	-	+	+	+	+		+
Other disturbances that may be included in the definition of dementia except for the Ischemic Scales	preserved	-	change	change	-	change	+	supportive features
Emotional lability	+	+	-	-	-	or +	-	supportive features
Somatic change(s)	+	+	-	-	-	-	-	-
Significant impairment in ADL and/or social functioning	-	-	NS	NS	NS	≥ 6 months	NS	NS
Symptom duration	+	+	+/+	+/+	+/+	+/+	-/+	+/+
Evidence of Significant CVD or Strokes								
Focal neurological signs/ symptoms	+	+	+	+	or +	+	or +	+
Evidence from history, examination or laboratory tests of significant CVD judged to be etiologically related to dementia	-	-	NS	NS	NS	supportive	or +	+
Structural imaging (CT scan or MRI)	NS	NS	+	+	+	+	≥ 2*	+
Multiple large vessel infarcts (cortex or angular gyrus or thalamus or basal forebrain)	NS	NS	-	-	-	-	+	+
One strategically placed infarct (cortex or angular gyrus or thalamus or basal forebrain)	NS	NS	-	-	-	-	+	+
Basal ganglia lacunes	NS	NS	+	+	+	+	+	+
White matter lacunes	NS	NS	+	+	+	+	-	+
Periventricular white matter lesions	NS	NS	+	+	+	+	-	+
Onset	-	-	+	+	+	≤ 6 months	+	≤ 3 months post-stroke
Temporal relationship between the CVD and onset of dementia	abrupt	abrupt	abrupt	abrupt	abrupt (or insidious)	abrupt or insidious	NS	abrupt or gradual
Type of onset	+/+	+/+	+/+	+/+	+/+ (or gradual)	or +/+	NS	+
Stepwise/fluctuating deterioration	-	-	+	+	+	+	NS	-
"Patchy" distribution of deficits								
Relationship between Dementia and CVD								
Progression	+	+	+	+	+	+	+	+

- Absent in the index criteria; + included in the index criteria

*or a single stroke with a clear temporal relationship to the onset of dementia and at least one infarct outside the cerebellum

HIS = Hachinski Ischemic Scale; IS-R = Ischemic Scale-Rosen; 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; MID = multi-infarct dementia; VaD = vascular dementia; IVD = ischemic vascular dementia; ADL = activities of daily living; NS = not specified; CVD = cerebrovascular diseases

TABLE 2. Additional Features Included in the Diagnostic Criteria for Vascular Dementia

ADDITIONAL FEATURES	HIS MID	IS-R MID	DSM-III MID	DSM-III-R MID	DSM-IV VaD	ICD-10 VaD	ADDTC IVD	NINDS-AIREN VaD
List of supportive features	—	—	—	—	—	(+) ¹	+ ²	+ ³
List of non-supportive features	—	—	—	—	—	—	+ ⁴	+ ⁵
Exclusion criteria	—	—	+	+	+	+	+	+
Delirium or confusion	—	—	—	—	—	—	—	—
Psychosis, severe aphasia, major sensorimotor deficit or other systemic disorders or other brain disease (i.e., AD)	—	—	—	—	—	—	—	—
Different levels of ascertainment (e.g., possible or probable or definite diagnosis)	—	—	—	—	—	—	+	+
Subtypes	—	—	(+) ⁶	(+) ⁶	(+) ⁷	+ ⁸	IVD-MIX	—

—Absent in the index criteria; + Included in the index criteria; (+) Included in the index criteria but not necessary

¹Associated features: hypertension, carotid bruit, emotional lability, depressive mood, transient episodes of clouded consciousness, often provoked by further infarction

²The diagnosis of probable IVD is supported by evidence of multiple infarcts in brain regions known to affect cognition; history of multiple transient ischemic attack; history of vascular risk factors, original HIS > 7 or IS-R ≥ 4. Clinical features thought to be associated with but require additional research include: gait disturbance and urinary incontinence; periventricular and deep white matter changes excessive for age, focal changes (electro)physiologic studies neuroimaging studies

³Clinical features consistent with the diagnosis of probable VaD include early gait disturbance; history of unsteadiness; early urinary symptoms; pseudobulbar palsy; personality and mood changes.

⁴Features that do not appear to constitute either strong evidence for or against the diagnosis of probable IVD: periods of slowly progressive symptoms; illusions, psychosis, hallucinations, delusions; and seizures. Features that cast doubt upon the diagnosis of probable IVD: transcortical sensory aphasia in the absence of corresponding focal lesions on neuroimaging studies; and absence of central neurologic symptoms/signs, other than cognitive disturbance.

⁵Features that make the diagnosis of VaD uncertain or unlikely include: early onset of memory deficit and progressive worsening of memory and other cognitive functions in the absence of corresponding focal lesions on brain imaging; absence of focal neurological signs, other than cognitive disturbance; absence of cerebrovascular lesions on CT or MRI.

⁶With delirium, with delusions, with depression, uncomplicated

⁷With delirium, with delusions, with depressed mood, uncomplicated; specify if behavioral disturbances

⁸Of acute onset, MID, subcortical VaD, mixed cortical and subcortical, other VaD, VaD unspecified

HIS = Hachinski Ischemic Scale; IS-R = Ischemic Scale-Rosen; 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; MID = multi-infarct dementia; VaD = vascular dementia; IVD = ischemic vascular dementia; MIX = mixed dementia

by a gradual decline. However, none of the DSM criteria mention the mandatory vascular brain lesions or an underlying vascular explanatory mechanism, clearly characterizing vascular dementia.

The ICD-10 The ICD-10 criteria define dementia as a progressive and unequal impairment of multiple higher cortical functions including memory impairment, deteriorations in general processing of information, and judgment and thinking (such as planning or organizing), but with preserved awareness. Deterioration from a previously higher level of performance should be established for a confident clinical diagnosis, and memory impairment should clearly be present for at least 6 months. Noncognitive features, such as deterioration in emotional control, social behavior, and motivation, may also accompany dementia. The ICD-10 criteria for vascular dementia require the presence of focal neurological signs and symptoms and evidence from history, examination, or tests of significant cerebrovascular diseases, which may reasonably be judged to be etiologically related to the dementia. The onset of dementia can either be abrupt, with a stepwise deterioration, or more gradual, and there must be an unequal distribution of cognitive deficits. These criteria also mention the existence of six subtypes of vascular dementia: acute onset, multi-infarct, subcortical, mixed cortical and subcortical, other, and unspecified dementias. Confirmation of the vascular etiology can be provided by CT, positron emission tomography (PET), MRI, or ultimately by neuropathological examination. Therefore, like the DSM criteria, the ICD-10 criteria have not detailed the mandatory vascular lesions that should be found using the brain imaging techniques.

The ADDTC Criteria The State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) criteria were initially designed specifically to diagnose ischemic vascular dementia.¹⁹ These criteria do not prioritize memory deficits over impairments of other cognitive functions. Instead, the authors of these criteria define dementia as "a deterioration from a known or estimated prior level of intellectual function sufficient to interfere broadly with the patient's customary affairs of life, which is not isolated to a single narrow category of intellectual performance, and which is independent of level of consciousness."¹⁹ Furthermore, for a diagnosis of *probable* vascular dementia, the ADDTC criteria require evidence of two or more ischemic strokes

(at least one infarct outside the cerebellum) by history, neurological signs, and/or neuroimaging studies (CT or T1-weighted MRI). In the case of a single stroke, a temporal relationship between the stroke and onset of dementia should be clearly documented, though the time interval between the two events is not specified. A diagnosis of *possible* vascular dementia is made when there is no clear temporal relationship between the single stroke and the onset of dementia or in individuals with clinical and neuroimaging evidence for Binswanger's disease. To meet the ADDTC criteria for *definite* vascular dementia, a histopathologic examination of the brain is required with pathological confirmation of multiple infarcts, with at least one infarct being outside the cerebellum. The criteria provide lists of features supporting the diagnosis of vascular dementia as well as features casting doubt on a diagnosis of probable ischemic vascular dementia (Table 2). Finally, the ADDTC criteria allow for a diagnosis of mixed dementia, applied when one or more systemic or brain disorder (thought to be causally related to the dementia) is present. The diagnosis of mixed dementia may thus include ischemic vascular dementia with Alzheimer's disease.

The NINDS-AIREN Criteria The National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) research criteria define dementia as a "cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains. The deficits should be severe enough to interfere with activities of daily living, and should not be due to physical effects of stroke alone."²⁰ Cerebrovascular disease is defined by the presence of focal neurological signs and evidence of relevant cerebrovascular diseases revealed by brain imaging. A relationship between dementia and cerebrovascular diseases is inferred by the onset of dementia within 3 months following a recognized stroke, or by an abrupt deterioration in cognitive functions, or a fluctuating, stepwise progression of cognitive deficits. No rationale has been provided to justify the choice of a 3-month interval between cerebrovascular diseases and the onset of dementia. The criteria also include lists of features consistent with the diagnosis, as well as features making the diagnosis uncertain or unlikely (Table 2). In addition, different levels of certainty for the diagnosis are defined. To meet the NINDS-AIREN criteria for *probable* vascular dementia, there must be a clear tem-

poral relationship between the onset of dementia and cerebrovascular diseases and confirmation of cerebrovascular diseases by cerebral imaging. The NINDS-AIREN criteria for *possible* vascular dementia include cases with no brain imaging data, or no clear temporal relationship between dementia and cerebrovascular diseases, or with an atypical course of dementia. Histopathological evidence of cerebrovascular diseases must be obtained at autopsy in the absence of any other neuropathological markers such as neurofibrillary tangles, neuritic plaques, or Lewy bodies to meet the NINDS-AIREN criteria for *definite* vascular dementia. The NINDS-AIREN criteria provide a list of potential locations for the vascular lesions in order to meet the criteria of vascular dementia (Table 1). Finally, the NINDS-AIREN criteria suggest that the term Alzheimer's disease with cerebrovascular diseases should be reserved to classify patients fulfilling the clinical criteria for possible Alzheimer's disease who also present clinical brain imaging evidence of relevant cerebrovascular diseases. According to the authors of these criteria, the term "mixed dementia" should be avoided.

Critical Issues

Defining the Cognitive Syndrome or Dementia The traditional Hachinski Ischemic Scale and its modified version, the Ischemic Scale of Rosen, did not include any definition of the cognitive syndrome. The DSM-III and DSM-IV criteria required anterograde or retrograde memory impairment, and the DSM-III-R criteria required *both* types of memory impairments in addition to one or more additional cognitive deficits (e.g., aphasia or apraxia) that collectively caused significant impairment in social/occupational functioning. The ICD-10 criteria required an unequal distribution of deficits in higher cognitive functions such as anterograde or retrograde memory and other cognitive deficits that interfered with activities of daily living *and* should have been present for at least 6 months. The NINDS-AIREN criteria included memory impairment (either in anterograde or retrograde memory) as well as deficits in two other cognitive domains, severe enough to interfere with activities of daily living. The ADDTC criteria did not specify the number or domains of cognitive function to be impaired, but instead proposed a significant progressive deterioration of multiple higher cortical functions.

Clearly, memory impairment is central in the definition of the cognitive syndrome of vascular dementia per

the DSM and NINDS-AIREN criteria, just as it is for the diagnosis of Alzheimer's disease per the DSM and NINCDS-ADRDA criteria.¹² The definition of the cognitive syndrome per the ADDTC criteria, because they are less stringent than the other criteria and do not specify any type of cognitive impairment, might perhaps best capture cognitive impairments caused by vascular risk factors,^{6,22,23} vascular lesions,²⁴ first-ever stroke,^{25,26} or vascular dementia.^{27–29}

Indeed, several studies have shown that vascular risk factors are related to cognitive impairment or decline with aging, especially in regards to psychomotor speed, executive function, and episodic and working memory.^{30–33} Other studies reported that patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy,²⁷ typical vascular dementia,²⁸ or poststroke dementia³⁴ presented with prominent executive dysfunction. Regarding the possible prodromal phase of vascular dementia, a recent study showed that patients with mild cognitive impairment-multiple domain tend to evolve to vascular dementia over 3 years in comparison with patients presenting with mild cognitive impairment of the amnesic type.³⁵

In their review, McPherson and Cummings³⁶ observed that most studies focusing on the cognitive deficits in vascular dementia had combined all patients with cerebrovascular pathology into a single group and suggested that observed "patchy" deficits may be an artifact of studying patients with various neuropathologic changes. Vascular dementia may thus result from a summation of pathologic processes. Moreover, a patchy and unequal neuropsychological profile is not specific to vascular dementia. Several neurodegenerative processes, such as dementia with Lewy bodies,^{37–41} semantic dementia, primary progressive aphasia, and frontotemporal dementia,⁴² differentially impact cerebral regions at a given level of disease severity. Finally, other reviews of vascular dementia concluded that executive dysfunction was more frequently found than memory and language deficits.^{43,44} However, these findings must be interpreted with caution due to possible inaccuracies in the determination of the dementia subtype and the loss of precision that might result from pooling heterogeneous subgroups of patients with vascular dementia; difficulties identifying a cognitive profile in patients who are required to present with memory impairment and other deficits to meet criteria for dementia; and the

use of limited test batteries whose psychometric properties are incompletely understood.⁴⁴

Finally, all criteria proposed delirium or confusion as exclusion criteria. Only the NINDS-AIREN, however, proposed stringent exclusion criteria such as clouding of consciousness, delirium, psychosis, severe aphasia, sensorimotor impairment precluding neuropsychological testing—which may result in the false exclusion of many cases of vascular dementia following stroke—and systemic disorders or other brain disease such as Alzheimer's disease that in and of themselves could account for deficits in memory and cognition (Table 2). When systemic disorders or other brain diseases such as Alzheimer's disease could have accounted for deficits in memory and cognition, only the ADDTC criteria provided the alternative of a mixed dementia diagnosis; the NINDS-AIREN criteria used the term "Alzheimer disease with CVD" instead.

Therefore, the lack of a clearly defined, evidence-based and consistently applied definition of the "cognitive syndrome" associated with vascular dementia, or more precise subtypes of vascular dementia, is likely to lead to a heterogeneous cohort of patients depending on which criteria are utilized.

Defining the Vascular Cause The most prevalent types of cerebrovascular diseases include large-vessel disease leading to multi-infarct dementia or strategic cortico-subcortical stroke, small-vessel disease leading to lacunar strokes and Binswanger's disease, cardiac embolic events, and hemodynamic mechanisms.^{45,46} However, the vascular lesions required to diagnose cerebrovascular diseases are not included in the clinical criteria for vascular dementia per the Hachinski and Rosen ischemic scales, the DSM-III, DSM-III-R, DSM-IV, and the ICD-10 criteria. The ADDTC criteria require at least two ischemic strokes outside the cerebellum or one infarct with a clear temporal relationship to the onset of dementia as measured by CT or T1-weighted MRI, whereas periventricular and deep white matter lesions were said to be potentially associated with ischemic vascular dementia. The NINDS-AIREN criteria required multiple infarcts (more than one cortical or subcortical lacunar infarcts) or extensive white matter lesions (detected by CT or T1-weighted MRI), but also accept strategically placed single infarcts as evidence of "relevant CVD." Notably, none of the eight clinical criteria mention the underlying mechanism of these vascular lesions (i.e., hemorrhagic versus occlusive) nor the location or

extent of required lesions. In conclusion, there is a need for clarity and consistency with regard to the nature of the vascular lesions which are required to be present for a diagnosis of vascular dementia and its subtypes. It is probable that different types of lesions are associated with different forms of vascular dementia and thus associated with different cognitive profiles and/or courses of illness. This issue will require consideration in future research.

Onset and Evolution of Vascular Dementia All the criteria, except for the ADDTC, require an abrupt onset with stepwise deterioration. The ICD-10 and NINDS-AIREN also specify a time interval between the cerebrovascular diseases and the onset of dementia (6 and 3 months, respectively). The DSM-IV, ICD-10, and NINDS-AIREN criteria mention that onset may be insidious or gradual. By contrast, the ADDTC do not specify the nature of onset and the pattern of deteriorating course, as patients with ischemic vascular dementia might experience a wide variety of natural histories. However, there is difficulty in establishing a temporal relationship between dementia and cerebrovascular diseases in terms of type of onset and evolution, which makes it difficult to properly identify patients with vascular dementia. Several data clearly suggest that some types of vascular dementia could start and develop in an insidious fashion without any clinically apparent stroke.⁴⁷ In particular, several patients with pathologically confirmed pure vascular dementia and most of those with both vascular dementia and Alzheimer's disease did not have clinical strokes that were temporally related to the onset of their dementia.⁴⁷ Moreover, prospective imaging studies demonstrated the occurrence of clinically silent infarctions.⁴⁸ Clinically silent cerebrovascular diseases, in the form of cerebral hypoperfusion, could produce hippocampal neuronal loss⁴⁹ or severe white matter pathological changes.⁵⁰ In addition, a clinical study of patients who met research and clinical criteria for vascular dementia revealed that fewer than 20% of family members described a stepwise pattern of cognitive decline.⁵¹ Again, consistency between diagnostic criteria, with regard to the natural history, onset, and evolution of the disease, is required.

Possible, Probable, and Definite Vascular Dementia In contrast to other criteria, both the ADDTC and NINDS-AIREN criteria proposed different levels of certainty for the diagnosis of vascular dementia, with the terms "pos-

sible" and "probable" and "definite" vascular dementia. Neuroimaging evidence of vascular lesions and autopsy validation are respectively required for a diagnosis of probable vascular dementia and definite vascular dementia. For these two sets of criteria the difference between a possible and a probable diagnosis lies in the absence versus presence of confirming cerebral imaging data, the number of cerebrovascular accidents (several of which are more related to probable dementia), and in a typical versus atypical (plateau or amelioration) course or evolution of the disease. However, the lack of consideration of subtypes of vascular dementia according to CT or MRI findings by several diagnostic criteria such as the DSM, ICD-10, Hachinski Ischemic Scale, and Ischemic Scale of Rosen still has an impact on current case detection.

Subtypes of Vascular Dementia According to Erkinjuntti,⁵² classification of vascular dementia may be based on the primary vascular etiology, the primary type of ischemic brain lesions, the primary location of brain lesions, and the primary clinical syndrome. However, the currently proposed subtypes of vascular dementia—multi-infarct dementia, subcortical vascular dementia and strategic infarct dementia—incorporate a variable combination of the given categories, thus reflecting heterogeneity in the diagnosis of vascular dementia. None of the current clinical criteria for vascular dementia include a detailed description of these subtypes. Indeed, the ischemic scales do not mention anything in this regard, whereas the DSM criteria do not specify any subtypes related to different cerebrovascular disease mechanisms, and the ICD-10 includes six poorly described clinical subtypes. According to the ADDTC criteria, the classification of ischemic vascular dementia should specify features of the infarcts that may differentiate the disorder (i.e., location, size, distribution, severity, and etiology) but only for research purposes. The NINDS-AIREN criteria list a series of stroke lesions that may be associated with vascular dementia (Table 1), but do not provide detailed descriptions of each subtype. Therefore, there is no agreement on a classification system for the vascular dementia subtypes. In fact, little research has been realized up to now comparing vascular dementia subtypes on important variables such as the pattern and severity of cognitive or functional impairment, the relationship to stroke risk factors, demographic variables, course of dementia, and cognitive syndrome.⁵³

Neuropathological Validation of the Diagnostic Criteria

There is currently an absence of widely accepted neuropathological markers of vascular dementia⁵⁴ as well as a heterogeneity in the pathological examination procedure used in various centers for diagnosing vascular dementia.⁵⁵ Another difficulty lies in determining, post-mortem, whether a vascular lesion was causal, contributory, or coincidental to the dementia.⁵⁶ Although there is a general agreement that some types of vascular lesions are associated with cognitive impairments,^{57–60} no consensus about the meaning of the term "vascular" has yet been reached, as is the case for the neuropathological characteristics of Alzheimer's disease.⁶¹ The ADDTC and NINDS-AIREN criteria only indicated a histopathological confirmation of the presence of multiple cerebral infarcts. Standards for the type, location, and extent of lesions required for vascular dementia or subtypes of vascular dementia are not yet agreed upon, whether it is for neuroimaging or autopsy findings. The degree to which infarcts or vascular lesions found in a patient contribute to dementia also remains to be determined. Moreover, in the field of neurodegenerative dementias, vascular lesions are frequently reported to be associated with Alzheimer's disease, exaggerating the cognitive deficits of both disorders⁶² and leading to a more rapid progression in Alzheimer's disease.⁶³ Mixed cerebrovascular disease and Alzheimer-type pathology are indeed common at postmortem, accounting for approximately 25%–35% of cases of late-onset dementia.⁶⁴ Cerebrovascular diseases lesions (i.e., cerebral amyloid angiopathy, endothelial and vascular smooth muscle degeneration, macroscopic infarction, microinfarction, hemorrhage, and white matter changes) are found in at least one third of patients with Alzheimer's disease, and pathological changes normally consistent with Alzheimer's disease are found in at least one third of patients with vascular dementia.⁶⁵ Therefore, the absence of clearly defined neurobiological markers of vascular dementia constitutes a major limitation of all current clinico-pathological studies, which impedes the "gold standard" verification of a vascular dementia diagnosis.

DISCUSSION

To our knowledge, this is the first qualitative review aimed at describing and comparing the symptom requirements of eight different clinical criteria used for the diagnosis of vascular dementia. Critical issues regarding

the definition of the cognitive syndrome and the vascular causes were differentially described in an effort to contrast them with current evidence reported in literature. To require the primacy of memory impairment in vascular dementia, an aspect not established on an empirical basis, induces problems that Looi and Sachdev²⁸ underlined a few years ago. These problems include: some patients with significant cognitive decline will not be diagnosed as having vascular dementia if their memory functioning is relatively well-preserved; in requiring memory impairment, the criteria may result in selection of the more severely cognitively impaired patients, precluding attempts at primary prevention; and the heterogeneity of cognitive impairment due to cerebrovascular lesions is likely to be underemphasized.

The reliability of the clinical diagnosis of Alzheimer's disease has partially derived from the predictable nature and location of its neuropathology,⁶⁶ which typically starts in the limbic system and affects episodic memory primarily and most severely. Such has not been the case with respect to the diagnostic criteria for vascular dementia. Neuropathological validation was seldom carried out before the implementation of the criteria. All these clinical diagnostic criteria have been consensus criteria that were neither derived from prospective community-based studies with clinico-pathological correlations of vascular factors affecting cognition nor based on detailed natural histories.^{67,68} In fact, the absence of a single, generally accepted, highly effective diagnostic methodology for vascular dementia clearly suggests a lack of consensus among clinicians and researchers,⁶⁹ and has made it very difficult to develop criteria for a prodromal state of vascular dementia. In addition, the available diagnostic criteria were all based on the ischemic infarct concept and have had limited validation.^{68,70} The specification of the neuropathological requirements for the diagnosis of vascular dementia and its subtypes may help to shed some light on the current controversy regarding the existence and nature of vascular dementia. Indeed, the absence of neuropathological criteria has led to skepticism about the existence of pure vascular dementia cases. Some authors believe that vascular dementia only exists along a continuum between Alzheimer's disease and vascular dementia⁶⁵ and that pure vascular dementia is rare, while others believe that Alzheimer's disease is a vascular disorder.⁷¹ More importantly, because Alzheimer's disease is more common in older people than vascular dementia, it is argued that the occurrence of stroke merely unmasks

latent Alzheimer's disease and calls attention to its subtle cognitive impairment that had not been recognized easily before the stroke. Both Tomlinson et al.⁷² and Hulette et al.⁷³ suggested that pure vascular dementia is uncommon at brain autopsy, and more recent neuropathologic findings showed that mixed Alzheimer's disease/vascular dementia is more common.^{74,75} Therefore, the cases of vascular dementia identified in the literature may result from mixed Alzheimer's disease/vascular dementia pathology and thus prove difficult to distinguish from Alzheimer's disease on neuropsychological testing.²⁸

This crucial debate may stem from the considerable heterogeneity in the concept of vascular dementia. Indeed, dementia may arise from a number of mechanisms and different vascular lesions as underlined above. The more prevalent types of cerebrovascular disorders (i.e., large artery disease, small vessel disease, cardiac embolic events, and hemodynamic mechanisms) may thus be associated with a particular neuropsychological profile and a particular course of illness. It is also possible that these different diagnostic criteria capture different thresholds or even subtypes of vascular dementia.⁷⁰ Therefore, it may be appropriate to abandon or at least narrow the classical concept of vascular dementia⁷⁶ by specifying cognitive profiles associated with different types of vascular conditions. Heterogeneous concepts such as vascular dementia with multiple sub-syndromes typically result in poor prognostic value and confusion in the literature especially from a neuropsychological point of view.⁷⁶ In addition, it is very unlikely that there will be one single treatment or one single prodromal cognitive stage associated with vascular dementia. Recently, it was suggested to divide vascular dementia into more homogeneous, predictable, and reproducible subtypes, which would improve the comparability between studies and be more practical in clinical settings than the current criteria.³ Erkinjuntti et al.⁷⁷ proposed to focus on subcortical vascular dementia and presented criteria in accordance with this subtype. This new classification incorporates small vessel disease as the primary vascular etiology, lacunar infarcts and ischemic white matter lesions as the primary type of brain lesions, subcortical location as the primary location of lesions, and frontal-subcortical syndrome as the primary clinical syndrome.³ Another suggestion would be to apply the concept of vascular dementia only to stable conditions in which progressive neuronal dysfunction due to vascular lesions or factors is associated

with a progressive overall decline in cognitive functioning (i.e., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy).⁷⁶ The stable conditions would be the chronic condition after a stroke or after a treatable infection, all cognitive domains being dependent on the location and nature of the underlying lesion.⁷⁶ In this case, the term poststroke dementia could be applied. These distinctions are important since both subcortical vascular dementia and poststroke dementia are easily identifiable in clinical settings⁷⁸—poststroke dementia because of an onset of cognitive decline in close temporal relationship with a transient ischemic attack or stroke event (although further refinement is needed because of various symptomatology and etiology) and subcortical vascular dementia because of the above mentioned reasons. A third and undoubtedly important subtype or “supertype” of vascular dementia, but much more difficult to identify than the first two subtypes, would be mixed Alzheimer’s disease/vascular dementia, presenting with heterogeneous clinical picture and etiology.⁷⁸

CONCLUSION

In conclusion, several sets of clinical criteria have been proposed to decrease subjectivity and disagreement among clinicians in establishing the diagnosis of vascular dementia. However, none of these criteria have been satisfactorily validated by longitudinal prospective

studies. Most of them depend on first diagnosing dementia using the Alzheimer-type criteria, based on memory deficits, upon which are superimposed vascular events, usually following a stroke model (i.e., abrupt onset, stepwise deterioration). This is probably inappropriate, as memory loss is not always prominent in vascular dementia, and strokes are not the only etiology of vascular dementia. Finally, there are no accepted and widely used neuropathological markers of vascular dementia or subtypes of vascular dementia. There is now a vital need for an international agreement on clinical criteria for the diagnosis of vascular dementia as well as subtypes of vascular dementia that would take into consideration the heterogeneous nature of the vascular mechanisms; the subtypes would be disease entities with their own typical pathological and clinical features, and would be responsive to particular therapies. The definition of the cognitive syndrome, as well as the method for its assessment, and the definition of the vascular causes, as well as their associated vascular lesions on cerebral imaging, are thus of crucial importance.

Dr. Wiederkehr is supported by a doctoral award from the Fonds de Recherche Québécois sur la Nature et les Technologies (FQRNT); Dr. Simard is supported by a 2005 NARSAD Young Investigator Award, and she is engaged in research funded by the Canadian Institutes of Health Research (CIHR). Part of this paper was presented at the 18th Annual Meeting of the American Neuropsychiatric Association, February 17–20, 2007, Tucson, Arizona.

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