National Institute of Neurological Disorders and Stroke–Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards

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Background and Purpose—One in 3 individuals will experience a stroke, dementia or both. Moreover, twice as many individuals will have cognitive impairment short of dementia as either stroke or dementia. The commonly used stroke scales do not measure cognition, while dementia criteria focus on the late stages of cognitive impairment, and are heavily biased toward the diagnosis of Alzheimer disease. No commonly agreed standards exist for identifying and describing individuals with cognitive impairment, particularly in the early stages, and especially with cognitive impairment related to vascular factors, or vascular cognitive impairment.

Methods—The National Institute for Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN) convened researchers in clinical diagnosis, epidemiology, neuropsychology, brain imaging, neuropathology, experimental models, biomarkers, genetics, and clinical trials to recommend minimum, common, clinical and research standards for the description and study of vascular cognitive impairment.

Results—The results of these discussions are reported herein.

Conclusions—The development of common standards represents a first step in a process of use, validation and refinement. Using the same standards will help identify individuals in the early stages of cognitive impairment, will make studies comparable, and by integrating knowledge, will accelerate the pace of progress. **(*Stroke.* 2006;37:2220-2241.)**

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One in 3 of us will experience a stroke, dementia or both, unless we do something about it.[1] Up to 64% of persons who have experienced a stroke have some degree of cognitive impairment,[2] with up to a third developing frank dementia.[3–5] Conversely, postmortem pathological studies[6–11] indicate that up to 34% of dementia cases show significant vascular pathology. Moreover, the same risk factors that make individuals prone to cerebrovascular disease also put them at risk for cognitive impairment.[12,13]

Cognitive impairment that is caused by or associated with vascular factors has been termed "vascular cognitive impairment" (VCI).[14–16] VCI can occur either alone or in association with Alzheimer disease (AD). Indeed, there appears to be a strong interaction between cerebrovascular and AD pathologies, such that individuals having both frequently show greater cognitive impairment than those having either pathology alone.[17–19]

Because vascular risk factors are treatable, it should be possible to prevent, postpone, or mitigate VCI, as well as the vascular exacerbation of AD. However, progress in VCI research has been hindered by lack of satisfactory diagnostic criteria for the condition. None of the current stroke scales

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measure cognition to any extent except for the Toronto Stroke Scale, which has never been used in clinical trials. Moreover, past diagnostic criteria for cerebrovascular disease–associated cognitive impairment have focused on the most extreme form of the condition, dementia. However, only about half the population of patients with VCI exhibit dementia,[20,21] and those who do not are better candidates for clinical trials because they are at earlier stages of their illness. Another problem with the focus on dementia is that the widely accepted definition of dementia requires memory impairment as an essential feature. This definition works well for identifying patients with AD, but often misses the executive dysfunction typical of cognitive disorders with vascular bases.[22]

As a first step toward developing diagnostic criteria for VCI, a workshop was convened by the National Institute for Neurological Disorders and Stroke (NINDS) and Canadian Stroke Network (CSN). It was recognized at the outset that our knowledge of VCI is currently still insufficient to develop a definitive checklist of diagnostic criteria for the condition. Rather, the goal of the workshop was to define a set of data elements to be collected in future studies aimed at more fully defining VCI, understanding its etiology, and identifying targets for treatment. Specifically, the participants were charged to do the following:

1. Develop screening questions that could be used to identify subjects with possible cognitive and behavioral impairment.

2. Establish a minimum dataset that would be useful in common clinical practice or large-scale research studies of VCI (eg, epidemiological studies, genetic studies or clinical trials), so that different studies could pool data for comparison and cross-validation.

3. Develop an "ideal" dataset for studies focused on particular research issues.

In addition, the participants were encouraged to suggest methods or scales for quantifying specific data elements, to identify which measures need to be validated, and to point out areas of promising research.

What follows represents a compilation of the recommendations of working groups in each of the following areas: Clinical/Epidemiology, Neuropsychology, Imaging, Neuropathology, Experimental Models, Biomarkers, Genetics, and Clinical Trials.

Clinical/Epidemiology Section

The Clinical and Epidemiology Group approached the issue of VCI from 2 perspectives. Initially, the working group outlined the items that should be considered in a population-based study of VCI. In particular, emphasis was placed on the variables that should be gathered in an ideal study. The second approach undertaken by the group was to develop an abbreviated, more clinically oriented evaluation. This set of recommendations includes a subset of variables from the previous exercise and is meant to be practically oriented for the clinician.

Population-Based, Epidemiological Approach

1. Demographics

The group felt that the minimum set of basic data to be gathered in a VCI study should include the following variables: sex; birthdate; race/ethnicity, including birth place of origin and parents' places of origin; years in the current country of residence; primary language; number of years of education; occupation; literacy; living situation and level of independence, including type of residence; marital status; handedness; and a contact person.

2. Informant (if available and determined relevant)

In taking information concerning the subject of interest, an informant should be sought if possible. The source of the information should be clarified as well as the amount and type of contact the person has with the subject. Additional data to be obtained should include the informant's birthdate, gender, ethnicity/race, relationship and length of time of relationship with the subject, education, and living status with respect to the subject.

3. Family History

A history of diseases in first degree relatives should be obtained. This history should include at a minimum information about past strokes, vascular disease including myocardial infarction, history of dementia, and other neurological diseases. For all of these items the age at death should be recorded, and the age of the event (eg, stroke) should be recorded.

4. Health History

Each subject should have a thorough health history obtained including information on cardiovascular disease such as myocardial infarction, arrhythmia/atrial fibrillation, angioplasty, stent, coronary artery bypass graft or valvular surgery, pacemaker, congestive heart failure, angina, and peripheral artery disease. For each of these, the question should be phrased to include, "Have you been diagnosed with _____?" "Do you have symptoms of _____?" Care should be taken to obtain this information on all of these medical conditions.

In addition, a history should be obtained on cerebrovascular disease including stroke (hemorrhagic or ischemic), transient ischemic attack, and endarterectomy. One should also inquire about other surgeries and, in particular, whether or not any cognitive difficulties arose after surgery. Finally, a list of all medications including over-the-counter preparations should be compiled.

Other factors to be included in the history include migraine, hypertension, hyperlipidemia, diabetes mellitus, sleep disorders, sickle-cell anemia, hypercoagulable states or related conditions such as deep-vein thrombosis, pulmonary embolus or spontaneous abortion, chronic infections such as periodontal diseases and bronchitis, autoimmune diseases, depression, substance abuse including tobacco and alcohol, diet, lifestyle, renal disease, menopause and the use of contraceptives, and environmental exposures such as second-hand smoke, pesticides, and medications (which should be classified by type).

5. Evaluation
Subjective symptoms and their onset should be recorded, including cognitive and behavioral symptoms, gait problems, tremor, balance, swallowing, incontinence, and pseudobulbar affect. In addition, vital signs should be collected, including height, weight, blood pressure (orthostatic), waist circumference, ankle-brachial index, heart rate, vision, and hearing. On the neurological examination, the NIH Stroke Scale (NIHSS) should be completed, as well as timed gait, motor movements, reflexes, and Babinski signs.

A discussion was entertained as to whether in this type of an exercise the physician's impression of cognitive impairment or vascular disease should be obtained, but this was not unanimously endorsed.

In addition, a mental status examination including components aimed at capturing vascular contributions to cognitive impairment should be completed (see the Neuropsychology Section below for recommended protocols), as well as a behavioral assessment such as the Neuropsychiatric Inventory-Q, a depression scale such as the Center for Epidemiological Studies-Depression (CES-D) or the Geriatric Depression Scale, and a functional scale such as the Pfeffer Functional Assessment Questionnaire or the Barthel Index.

Although this is not an exhaustive set of suggestions, these items were believed to be pertinent in an epidemiological study that might identify individuals with cognitive impairment.

Abbreviated Clinical Evaluation

It was also requested that the Clinical and Epidemiology Work Group make recommendations for an abbreviated clinical examination that could be performed in the context of a busy primary care physician's practice. As such, the following subset of the above recommendations was suggested.

1. Demographics
The minimum data set should include sex, birthdate, race/ethnicity and education.

2. Informant
If available and deemed to be necessary, basic information regarding the informant's demographics as mentioned above and the time and quality of the contact with the subject should be obtained.

3. Family History
History information concerning first degree relatives for a history of stroke, vascular disease or dementia should be obtained.

4. Health History
Historical questions concerning cardiovascular or cerebrovascular conditions, hypertension, hyperlipidemia, diabetes mellitus, alcohol use, tobacco use, physical inactivity, and medications should be obtained.

5. Evaluation
The subjective impression of the individual being evaluated should be sought with regard to the person's general health, including whether, during the past year, the person has experienced changes in memory, speed of thinking and acting, or mood. Information should be obtained regarding functional abilities that include instrumental activities of daily living.

On the examination, a physical examination should be done to collect vital signs and other data including height, weight, blood pressure, waist circumference, and timed gait. A mental status examination which focuses on vascular impairment should be done. This evaluation should include an assessment based on the clinical judgment of the examiner with respect to cognitive impairment and vascular contribution. However, as noted previously, the utility of such subjective, qualitative evaluations remains to be determined.

Finally, in the setting of an investigational study, certain laboratory studies should be done. These would include: collecting serum, plasma, and DNA for possible cell lines, ECG, cardiac echo, carotid ultrasound, urine studies and a MRI of the head. With respect to serum or plasma markers, the following measures could be considered: C-reactive protein, lipids, homocysteine, glucose, hemoglobin A1C, insulin, clotting factors, and fibrinogen.

Neuropsychology Section

Preamble and Criteria for Test Selection

VCI encompasses a large range of cognitive deficits, from relatively mild VCI no dementia to more severe vascular dementia, or combined cerebrovascular disease with other dementing conditions, such as AD.[23] The pattern of VCI cognitive deficits may include all cognitive domains, but there is likely to be a preponderance of so-called "executive" dysfunction, such as slowed information processing, impairments in the ability to shift from one task to another, and deficits in the ability to hold and manipulate information (ie, working memory).[24–26] Neuropsychological protocols must therefore be both sensitive to a wide range of abilities *and* especially attuned to the assessment of executive function. Timed executive function tests may be especially sensitive to VCI-related impairment because of the slowed information processing noted in this patient sample.

The Neuropsychological Working Group was charged with recommending test protocols that could be used in multicenter investigations of potential patients with VCI. Because different protocols serve different purposes, the working group was requested to produce 3 separate protocols, one that required ≈60 minutes, a second that required 30 minutes, and a third that required 5 minutes. It was envisioned that the 60-minute protocol be developed for use in studies that require a breakdown of cognitive abilities by domain, so the protocol contains recommended tests in 4 domains: executive/activation, language, visuospatial, and memory. In addition, tests were selected to examine neurobehavioral change and mood. Tests for the 30-minute protocol were selected from within the 60-minute protocol to be used as a clinical screening instrument for patients with suspected VCI. Finally, a 5-minute protocol was devised for potential use by primary care physicians, nurses and other allied health professionals, who need a quick screening in their office or at

TABLE 1. Neuropsychological Test Criteria

Quality of the standardization sample
Psychometric qualities
Portability
Brevity
Cost
Ease of use
Domain specificity (for 1-hour battery)
Availability of multiple forms
International or cross-cultural capability
The lack of ceiling and floor effects
Previous use of the test in VCI samples

the bedside. The 5-minute protocol was also designed for very large epidemiological studies or clinical trials in which sensitivity and ease of administration are especially important. In addition, the 5-minute protocol was designed so that, once validated, it would be possible to be administered by telephone.

The working group was set up as an expert panel that considered the benefits and limitations of potential protocol instruments. In making its decision, the working group referred to prespecified test criteria (Table 1). It was recognized that there were no perfect tests. Instead, tests selected for inclusion in the protocols met a preponderance of the criteria. In addition, high priority was given to executive control, activation state and processing speed, word retrieval and episodic memory, to help differentiate VCI from AD and to target the executive domain.

Proposed Neuropsychological Test Protocols

In order to maximize information obtained from a relatively brief number of tests, conventional well-validated tasks were selected. A number of novel analyses were proposed whereby multiple measures could be derived from a single simple short test. For example, word list generation cued by category can provide information relevant to language, activation, and speed of processing, set shifting, working memory and executive control.[27,28] Hence, one brief test can provide useful insight into different domains. In other words, economizing on time for administration can still yield, through neuropsychological "post-processing", multiple cognitive measures probing different anatomical regions and brain networks. A listing of the proposed 60-minute protocol tests, along with their primary citations and suggested normative sources is found in Table 2. The proposed 30-minute and 5-minute protocols are listed in Table 3.

A. 60-Minute Protocol

1. Executive/Activation

Theoretical Framework for Fractionating Frontal Lobe Function. It has been posited that functional domains within the frontal lobes can be fractionated, based on a theory of the evolution of 2 cortical architectonic trends, a dorsal (executive-cognitive) and a ventral (emotional-self regulatory) trend.[29,30] The "archicortical" trend evolves from the hippocampus and involves the dorsolateral prefrontal cortex, which mediates spatial and conceptual reasoning processes.

TABLE 2. Sixty-Minute Protocol: Test List, Citations and Suggested Potential Standardization Sources

	Citation	Suggested Standardization Sources
Executive/Activation		
Animal Naming (semantic fluency)	35	167–169
Controlled Oral Word	39, 40	170, 171
Association Test		
WAIS-III Digit Symbol-Coding	45	45
Trailmaking Test	47	169, 170, 172
List Learning Test Strategies		
Future Use: Simple and		
Choice Reaction Time		
Language/Lexical Retrieval		
Boston Naming Test 2nd	55	170, 173
Edition, Short Form		
Visuospatial		
Rey-Osterrieth Complex	51	54, 174, 175
Figure Copy		
Supplemental: Complex	51	54, 174, 175
Figure Memory		
Memory		
Hopkins Verbal Learning	61	61
Test-Revised		
Alternate: California Verbal	64	64
Learning Test–2		
Supplemental: Boston		
Naming Test Recognition		
Supplemental: Digit Symbol-	46	46
Coding Incidental Learning		
Neuropsychiatric/Depressive Symptoms		
Neuropsychiatric Inventory	65	65, 176, 177
Questionnaire Version		
Center for Epidemiological Studies-Depression Scale	66	67
Other		
Informant Questionnaire for	74	74
Cognitive Decline in the		
Elderly, Short Form		
MMSE	75	

The "paleocortical" trend, which mediates emotional processing, such as stimulus-reward associations, emerges from the orbitofrontal (olfactory) cortex and is linked to limbic nuclei such as the amygdala. Two additional specialized functions within the prefrontal cortex have developed later in human evolution, including action-regulation by the superior medial frontal region[31] and metacognitive functions that appear to be subtended by the frontal polar regions, particularly on the right side.[32–34]

Test Selection. Test procedures in the Executive/Activation domain were selected to sample these various functions. First, the working group adopted both a category (semantic) and a

TABLE 3. Proposed 30-Minute and 5-Minute Neuropsychological Protocols

30-Minute Test Protocol
Semantic Fluency (Animal Naming)
Phonemic Fluency (Controlled Oral Word Association Test)
Digit Symbol-Coding from the Wechsler Adult Intelligence Scale, Third Edition
Hopkins Verbal Learning Test
Center for Epidemiologic Studies-Depression Scale
Neuropsychiatric Inventory, Questionnaire Version (NPI-Q)
Supplemental: MMSE, Trail Making Test
5-Minute Protocol
MoCA subtests
5-Word Memory Task (registration, recall, recognition)
6-Item Orientation
1-Letter Phonemic Fluency

Supplemental: Remainder of the MoCA, Semantic Fluency (Animal Naming), Trail Making Test, MMSE (to be administered at least 1 hour before or after the above tests).

letter (phonemic) fluency test. The category fluency test chosen was "Animal Naming"[34–37] because of its common use, especially in elderly clinical populations, the availability of multiple normative sets, and the relative ease of potential cross-cultural applications. The test is included as part of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological assessment battery.[38] The letter fluency test chosen was the Controlled Oral Word Association Test.[39,40] This test includes 2 sets of 3 letters (CFL and PRW) that are of similar difficulty and can be used interchangeably. Multiple normative samples are available.

Both category and letter fluency tasks were chosen because of research suggesting differential performance in clinical populations across the 2 tasks and the potential of identifying separate executive as well as domain-specific (eg, language) processes.[27,28,35,37,41–43] The working group recognized that there is a cultural generalizability issue with phonemic fluency tasks, as they would not be applicable to nonphonetic languages. Cueing by initial sounds of words rather than by letter might be appropriate in these languages, but would need to be developed and validated, if this were feasible. Similarly, letters differ in the frequency of their use across languages and we recommend that non-English investigators who wish to use the phonemic fluency task choose letters with roughly the same frequency of use in the alternate language as CFL and PRW are used in English.

Both of the fluency tasks will be administered and scored in the standard manner. However, additional scoring options may lead to a richer understanding of frontal executive functions. For example, the number of words generated in the first 15 seconds of a 1-minute word-list generation task reflects more automatic processing and provides an index of speed and activation.[43,44] The number of words generated in the subsequent 45 seconds yields information on working memory, set shifting and executive control, obtainable through careful analysis of the strategies used to cluster words. Category cueing, such as animals or fruits, may rely on posterior left parietal-temporal functioning,[27] whereas phonemically-cued word-list generation has demonstrated relationship with left dorsolateral frontal integrity.[43]

In addition to the fluency tasks, the working group chose to include the Digit Symbol-Coding subtest from the Wechsler Adult Intelligence Scale, Third Edition.[45] This task provides a direct measure of processing speed and activation. Additional supplemental tasks of incidental free and cued recall are available for this task.[46] The Trailmaking Test[47]was also chosen to provide an additional measure of information processing speed and set shifting.[32] Finally, the working group recommends that additional scoring options available from the revised Hopkins Verbal Learning Test (HVLT-R) can provide measures of strategic learning reflecting dorsolateral frontal function, in addition to episodic memory indices.[48–50] By examining the strategies used to learn a super-span list, a measure of executive organization can be derived.

Test procedures to probe self-regulatory functions and metacognitive processes are still in development, but these behaviors can be inferred through the use of questionnaires, administered to caregivers. Likewise, the working group recommends that both simple and choice reaction time tasks should be considered as additions to the protocol in the future, because such activation tasks have been shown to be sensitive to frontal executive function, but as of yet may be cost prohibitive and require special equipment. As part of the validation process for the test protocols, we recommend the completion of exploratory and confirmatory factor analyses. These analyses may point toward a bifurcation of Executive/Activation tasks into timed and untimed tests.

2. Visuospatial

The working group selected the Rey-Osterreith Complex Figure[51] copy condition as the primary visuospatial test. The memory condition of the test was selected as a supplemental measure. This well-known, untimed spatial task requires both organizational and visuoperceptual skill. Multiple scoring systems are available, including a standard 36-point method of determining accuracy of the final product[52,53]and more qualitatively based systems that include a study of subject's organizational ability.[54] Standardization samples are available for the major scoring systems.

3. Language/Lexical Retrieval

The working group chose the Short Form (15 item) of the Boston Naming Test (BNT), Second Edition, as a measure of visual confrontation naming. The BNT, which is associated with the Boston Diagnostic Aphasia Examination,[55] has been well studied. Shorter versions, using either 15 or 30 words, have been found mostly equivalent and are relatively reliable and valid as screening tests, with age and education effects varying in different studies.[56–58] The correlation between the Short Form and the 60-item BNT is 0.97.[55] Normative information is exclusively based on the 60-item version, and it is suggested by the authors to extrapolate this information for the 15-item version.[55] As mentioned above, "animal" fluency can serve as a less structured lexical retrieval task as well as that of a test of executive function. Verbal fluency tasks have been widely used for many decades with some discriminative value in differentiating cognitive impairment and dementia from normal aging as well as VCI from AD.[59,60]

More detailed tests of semantics and syntax including the Pyramids and Palm Trees Test and the Token Test were considered but not included in the basic battery. These could

be supplemental tests to probe comprehension and semantic understanding more thoroughly. Similarly, a test of apraxia was considered but not included at this time because of the expertise required in scoring and lack of available validated batteries. Apraxia testing could be considered for future use if an appropriate brief tool were available.

4. Memory/Learning

The working group favored a list-learning test over a paragraph-recall test or a paired association–learning test because list-learning tests can generate acquisition scores initially and with repeated administration, as well as a short- and long-delayed recall. In addition, list-learning tests are easier to develop in other languages and cultures than paragraph-recall tests.

After much debate, the HVLT-R[61] was chosen as the preferred list-learning test. Strengths of the HVLT-R include its multiple alternate forms, its use in clinical trials and its relatively brief administration time. The working group recognized that the HVLT-R does not include either an interference list or a cued recall condition, both of which have been found to be sensitive to VCI-related cognitive impairment in clinical samples.[60,62,63] For this reason, the working group includes the California Verbal Learning Test, Second Edition (CVLT-2[64]), as an alternative to the HVLT-R, which may be used by investigators who require the additional information gained from this test (eg, cued recall), who are studying subjects capable of completing a 16-word list test, and who have the increased time necessary to complete the CVLT-2.

In addition to either the HVLT-R or the CVLT-2, the working group recommended the development of a brief test of recognition memory created by repeating the BNT items with foils in a forced choice picture recognition paradigm. Cued recall of the pairing of the symbols and numbers in the Digit Symbol-Coding test can also be completed.[46]

5. Neuropsychiatric/Depressive Symptoms

The working group recommended the Neuropsychiatric Inventory, Questionnaire Version.[65] This test is derived from the original NPI, but can be completed by a caregiver without the need for an interviewer. The test probes most behavioral domains that are affected in VCI as well as other disease conditions. In addition, in order to more thoroughly probe depressive symptoms, the working group recommends the Centre for Epidemiologic Studies-Depression Scale (CES-D) developed at the National Institute of Mental Health.[66] It has 20 items, takes about 10 minutes and can be self-reported or administered as a questionnaire by an examiner. The CES-D has been used for over twenty years and has been previously validated in NINDS Stroke Data Bank patients using a structured psychiatric interview and established diagnostic criteria: a score of 16+ had been found to be highly predictive of clinical depression (sensitivity 86%, specificity 90%, positive predictive value 80%).[67] It has been shown to have high concurrent validity with other depression measures in geriatric stroke patients (both observer-reported and self-reported)[68] and has been used to assess poststroke depressive symptomatology in several studies.[68,69] It has also been used in the Cardiovascular Health Study.[70] In addition to the examination of depression and if time permits, investigators may consider completing a measure of apathy, such as Starkstein's Apathy Scale[71] in light of studies demonstrating apathy in patients with suspected VCI.[72]

6. Premorbid Status

To obtain premorbid history of cognitive status, the 16-item Informant Questionnaire for Cognitive Decline in the Elderly[73,74] should be completed by a person knowledgeable of the patient.

The Mini-Mental State Examination (MMSE[75]) is widely used in all dementia studies and would be a sensible supplement to the above protocol.

B. 30-Minute Protocol

Already available batteries such as the modified MMSE[76] and Cognitive Abilities Screening Instrument[77] were considered because they have been used in population studies of the elderly and dementia. However, the concern was their sensitivity in a VCI context. Hence, a subset of the 60-minute protocol for screening purposes was suggested to include semantic and phonemic fluency, Digit Symbol-Coding and the revised Hopkins Verbal Learning Test, in addition to the CES-D and Neuropsychiatric Inventory. The Trail Making Test A and B could be used as a supplemental measure and MMSE would also be prudent if not already administered.

C. 5-Minute Protocol

There was considerable debate as to whether or not MMSE would be sufficient for a brief, minimal data set. However, this was rejected because it insufficiently probes executive function and because its 3-word recall test may be insensitive to the more subtle memory impairment often encountered in VCI. It was also felt that it would be advantageous if this brief protocol could be administered by telephone. The recommended protocol consists of selected subtests from the Montreal Cognitive Assessment available with instructions and sample means in English and French at www.mocatest.org (MoCA[78]), including a 5-word immediate and delayed memory test, a 6-item orientation task and a 1-letter phonemic fluency test (the letter F). The MoCA may be used without permission, free of charge, for clinical or educational noncommercial purposes (Copyright Ziad Nasreddine, MD).

Supplemental tests, not all of which would be amenable to telephone administration, could comprise all or part of the remainder of the MoCA, which includes a cube and a clock drawing task with a simple scoring routine, a 3-item picture naming task, a short "Trails B" paradigm and other brief attention, language and abstraction tasks, and would take an additional 5 minutes. If there is more time available, some investigators may also wish to complete the original Trail-making Test,[47] a semantic fluency test or the MMSE, provided that the MMSE is completed on a different day or an hour or more after the 5-minute protocol if done on the same day.

Summary

It is important to note that that these protocols are offered as a basic assessment, appropriate for different purposes. Supplemental tasks can be used on a project basis and if further

emphasis is needed on particular functions. Validation of the protocols needs to be completed to see how well they detect documented cognitive impairment and how well they do so in relation to cerebrovascular disease. In particular, the 5-minute protocol, and the supplementary items from the MoCA, will require further age and education standardization in English and French as well as other languages. Further standardization would also be needed for the phonemic fluency in nonphonetic languages such as Chinese, and for the brief test of recognition memory using items from the short BNT with suitable foils. The goal is to encourage all comers—clinicians, epidemiologists, vascular medicine and dementia researchers alike—to consider the use of the recommended tests to obtain minimal cognitive data sets, according to the particular application, in order to improve communication, comparability and dialogue across cultures, patient groups, and studies and achieve better understanding and treatment of VCI around the world.

Neuroimaging

Neuroimaging in Studies of VCI

The main role of neuroimaging in the study of VCI so far has been to describe the brain, not diagnose it. Thus, neuroimaging plays a fundamentally different role in the study of VCI than it does in other conditions.[79,80] This focus on description rather than diagnosis results from the facts that (1) vascular and degenerative pathology frequently coexist,[9] and (2) there are no pathognomonic radiological features of VCI. Different researchers have used a variety of terms and definitions to describe the changes in the brains of people with VCI, making comparison between studies difficult; this in turn has limited the understanding of the neuroimaging features of this condition. The use of a common minimal research data set with standardized terminology in all clinical studies can help overcome this obstacle. A minimal data set does not preclude researchers from adding their own neuroimaging descriptors. Rather, it simply stipulates those variables that must be

TABLE 4. Imaging: MRI Measures

Feature	Recommended MRI Measure	Acceptable MRI Measure
Brain atrophy	• Quantitative measurement of brain volume normalized for head size	• Estimates of Atrophy and Ventricular Size using the CHS Scale [88] • Estimates of Medial Temporal Lobe Atrophy using Scheltens Scale[87]
White Matter Hyperintensities (WMH)	• Quantitative measurement of WMH volume normalized for head size • Anatomical mapping also encouraged[85]	• Preferred: ARWMC scale[89] • Also Acceptable: CHS WMH scale[88]
Infarction	• All infarcts should be localized using a standard approach to generate quantitative measures of volume and location. Ideally, identified infarcts would also be mapped to a common stereotatic space[85] • All infarcts should be further differentiated from perivascular spaces by CHS criterion (see Table 2) independent of method to determine size and location	• No. and size at specified locations Size (largest diameter): Large> 1.0 cm Small 3 mm-10 mm • Location*: Anatomical locations Supratentorial Hemisphere Cortical (may include subcortical) Exclusively Subcortical white matter Exclusively Subcortical gray matter Infratentorial * Encourage use of Talairach atlas[85] for precise anatomical localization
Hemorrhage	• All lesions should be localized using a standard approach to generate quantitative measures of volume and location. Ideally, identified lesions would also be mapped to a common stereotatic space[85]	• No. and size in each locations Size (largest diameter) Large hemorrhage>1cm in diameter Microhemorrhage¶: < 1 cm Susceptibility on gradient echo Must report lower size limit cut-off, field strength Criterion in development and further work is necessary • Location Same as infarcts
Other	Mass lesions, AVMs, extra-axial fluid collections, malformations, dysplasia or any other lesion that might complicate assessment of cerebrovascular disease	

TABLE 5. Imaging: CHS Lesion Scoring

	White Matter		
	T1	FLAIR/Proton Density	T2
Perivascular Space	Decreased	Isointense	Increased
Ischemic Change	Isointense	Increased	Increased
Infarct	Decreased	Increased	Increased
	Gray Matter		
	T1	FLAIR/Proton Density	T2
Perivascular Space	Decreased	Isointense	Increased
Ischemic Change	N/A	N/A	N/A
Infarct	Decreased or Isointense	Increased	Increased

TABLE 6. Imaging: CT Measures

Ventricular size*
Hippocampus: medial temporal atrophy[90]
Diffuse white matter: ARWMC[89]
Discrete hypodensities
(CSF density; consistent with infarction or old hemorrhage)
>3 mm-1.0 small
>1.0 large
No., volume, location same as MRI
Acute hemorrhage

*Needs scale with adequate validation.
CSF indicates cerebrospinal fluid.

measured and shared by all investigators. Implementation of this standard will allow comparisons between studies (population enrolled, outcome) and facilitate the pooling of data across research groups.

Prospective studies of VCI must include measures of ischemic brain injury as well as AD-type pathology, a prevalent confounder of brain-behavior relationships in VCI.[17,81] Whereas quantitative measurements are ideal, reliable qualitative scales may provide important data for large cohort studies. Before these scales can be accepted, however, intra- and interobserver reliability must be established, and the new scale must be validated against quantitative measurements. In addition, the means of conversion to existing scales need to be determined.[82]

MRI is the ideal imaging tool for cognitive disorders because it is the most sensitive modality, and it offers the greatest amount of reliable data. The minimally acceptable field strength is 1.0 T, but 1.5 T or greater is preferred. The following sequences are required: 3D T1-weighted, T2-weighted, fluid-attenuated inversion recovery, and gradient-echo. The first 3 sequences provide information on the anatomy and presence of infarction and other pathology, whereas the latter detects large and small, acute and chronic hemorrhages.[83] In addition, diffusion-weighted images, and quantification of the apparent diffusion coefficient is encouraged because it gives information about acute strokes and integrity of the white matter fibers.[84] Images must be acquired parallel to the AC-PC line, which goes from the superior surface of the anterior commissure to the center of the posterior commissure.[85] CT has limited use in VCI research because it measures only severe disease, the findings are difficult to quantify, and there is significant radiation exposure (especially if 2 or more scans are obtained). Two general CT techniques can be used: the axial acquisition at +15° to the orbital-meatal line, and hippocampal acquisition at −30° to the orbital-meatal line, using 2-mm slice thickness.

Table 4 lists the recommended and acceptable MRI measures for prospective studies of VCI, and Table 5 lists the signal characteristics that differentiate perivascular space and infarcts, as used in the Cardiovascular Health Study (CHS).[86] The use of these standardized definitions is encouraged. Volume measurements, normalized for head size to take into account gender effects, are recommended to quantify atrophy and white matter hyperintensities, but validated qualitative scales are also acceptable.[87,88] The size and location of infarcts and hemorrhages must be specified,[85] preferably using standardized atlases, as described in Table 4. Table 6 lists the information that can be obtained from CT scans. Qualitative and quantitative scales of ventricular size have to be developed and validated. Hippocampal atrophy and white matter hyperintensities can be described using qualitative scales.[89,90] In the chronic stage it is difficult to differentiate hemorrhages from infarcts, as both appear hypodense; for this reason, the number, volume, and location of discrete hypodensities, rather than infarcts and hemorrhages, should be described. Acute and subacute hemorrhages are clearly different from infarcts and should be described as such.

Retrospective studies based on chart abstraction of radiological reports are of limited value because radiological reports seldom have sufficient detail. Whereas certain imaging features are frequently mentioned in clinical reports (eg, "age appropriate atrophy", "white matter changes of vascular origin"), these are not sufficiently reliable for clinical research studies and, thus, should not be recorded, because they are only confounding information. Data to record are the presence of large infarctions, small subcortical infarctions, acute hemorrhage, ventricular enlargement, and other pathology.

Other neuroimaging techniques and applications require further research before they can be used routinely in prospective studies of VCI. The areas for further research are detailed in Table 7.

Neuropathology

Optimal Brain Handling and Processing at Autopsy

The pathological diagnosis of VCI requires systematic evaluation of potentially relevant features. To achieve this, there must be some uniformity of autopsy protocols across centers, although individual approaches can be based on the strengths of a particular program. A large number of centers may follow the Alzheimer's Disease Research Centers, USA (ADRC) guidelines, in which 1 cerebral hemisphere (usually left) is fixed and the other hemisphere frozen. If this approach is used, it is important to realize that lesions in the frozen

TABLE 7. Imaging: Areas for Further Research

I. Existing techniques that provide further valid descriptive data about the brain and the cerebral vessels, but the data are not considered to be essential descriptors

a. Status of the cerebral vasculature

1. Large extracranial vessels measured by carotid intimal-medial thickness (IMT)
2. Estimate of extracranial internal carotid stenosis with measurement technique validated by angiography at participating institution
   i. Please see note in III.b0.7.i for discussion of issues surrounding vascular imaging of intracranial vessels

b. White Matter Disease

1. Diffusion Tensor Imaging for measures of diffusivity or fractional anisotropy[178, 179]

c. FDG PET and Perfusion SPECT for the exclusion of AD

1. These techniques have high negative predictive value for AD and can be used to identify subjects without temporo-parietal hypometabolism/hypoperfusion in whom the chance of the co-occurrence of AD is low.[180] The positive predictive value of temporo-parietal hypometabolism/hypoperfusion for AD in subjects with ischemic brain damage is unknown

II. Existing techniques with potential application but requiring further study

a. High priority areas for further study because of potential importance

1. FDG PET/Perfusion SPECT in mixed disease
   i. For the identification of AD pathology in subjects with CVD
2. Amyloid PET imaging #
3. Retinal vessel imaging

b. Lower priority for further study because of unclear potential importance

1. Cortical gray matter atrophy
2. Basal ganglia/Midbrain atrophy measurements and other regional atrophy measures

III. Areas of future research development

a. Technology not yet available, but high priority for development because of potential importance

1. Intracranial small vessel imaging
2. Cortical microscopic infarct imaging
3. Differentiation of hippocampal sclerosis
4. MR molecular imaging

b. Existing technologies of unclear value in VCI

1. Transcranial Doppler detection of emboli (High Intensity Transient Signals)
2. Functional MRI
3. Blood Brain Barrier integrity
4. MRI Spectroscopy
5. Vascular reactivity
6. Perfusion imaging
7. Intracranial large vessel imaging

i. Intracranial vascular imaging is currently in development. Current data suggest that MRA has high specificity, but low sensitivity when compared to cerebral angiography[181]. In addition, there is considerable variability in performance within even single centers. Therefore, this or other MRI techniques require further investigation. CT angiography is more sensitive and has high specificity as well in experienced hands,[182] but there are issues with applicability for clinical research because of radiation exposure and contrast side-effects.

hemisphere may be missed. Therefore, it is recommended that centers fix and freeze alternate coronal blocks from each cerebral hemisphere. Centers with major interests in neuroimaging correlative studies may prefer most of the brain to be fixed. Nonetheless, it is recommended that all centers should snap-freeze at least some material to obtain good quality mRNA, even with long postmortem intervals between death and freezing of tissue. The quality of the mRNA and viable yields aquired can be assessed case by case.[91] Sampling of fixed brains should follow the CERAD protocol and include anterior (centrum semiovale) and posterior white matter blocks.

Assessing the neuropathological substrates of VCI obviously involves assessment of (1) parenchymal lesions, including infarcts and hemorrhages, and (2) the vascular abnormalities that may have caused them. The vascular lesions that contribute to full-blown dementia syndromes (during life) often show much more severe abnormalities than those contributing to milder VCI.[92–94] In addition, systemic factors (eg, hypotension, hypoglycemia) may cause brain lesions in the absence of severe vascular disease. Finally, parenchymal abnormalities may be present that are not obviously associated with either vascular disease or systemic factors; these include Alzheimer or hippocampal lesions.

The National Alzheimer's Coordinating Center (NACC; www.alz.washington.edu) vascular dataset is a reasonable starting point for guiding one in the assessment of cerebrovascular disease, but could be refined to be more informative.

The guidelines below will differentiate between a "minimal" informative dataset, and an "ideal" dataset for each type of abnormality being considered.

Data to Be Collected

1. Atherosclerosis of the Basal, Peripheral and Meningeal Vessels

Minimal Dataset

Comment should be made on the severity of basal atherosclerosis. Optimally, one should photograph this, especially noting similarities and differences between the anterior versus posterior portions of the circle of Willis, and left versus right sides. Representative histologic sections of the major arteries could be provided. The presence and severity of dolichoectasia and fusiform aneurysm(s) should be noted. Severity of stenosis of major arteries should be assessed, and can easily be estimated in 'quartiles', 0 to 25%, 26% to 50%, 51% to 75%, etc. The presence of atherosclerosis in distal (meningeal) arteries should be assessed.

Ideal Data Set

Further information from antemortem data on atherosclerosis of the cervical arteries may be acquired from angiographic studies. Severity of atherosclerotic lesions may be verified by dissecting the carotid and vertebral arteries in the course of a complete necropsy. This is more practical (though time-consuming) for the carotid than vertebral arteries; in practice it is rarely done. The status of the vessels in the heart, kidneys and other vascular beds should be assessed in the course of a complete autopsy. In addition, histological sections should be obtained to assess atherosclerosis, including plaque calcification, hemorrhage (remote or recent), ulceration, mural or complete thrombi, etc, as well as changes in distal arteries (eg, over the cerebral convexities).

2. Microvascular Disease: Arteriosclerosis

In general, arterial disease is considered more significant than venous disease. Venous adventitial fibrosis should be evaluated, however, because it has been linked to cognitive abnormalities and neuroradiologic lesions in some studies.[95,96] Areas to sample are those specified in the CERAD protocol,[97] together with anterior and posterior white matter blocks from the frontal and parieto-occipital regions, respectively. The middle cerebral artery-anterior cerebral artery watershed zones bilaterally are appropriate regions to assess for watershed ischemic change, and also to screen for cerebral amyloid angiopathy (CAA).

Minimal Data Set

Assessment of the severity of arteriosclerosis can be quite subjective. To minimize this subjectivity, templates are best used and findings in a tissue section matched to these (Ann McKee, personal communication, 2005). Any degree of inflammation should be documented, including presence of lymphocytes or macrophages centered on blood vessels (and not necessarily a function of brain ischemia). Perivascular hemosiderin should be noted as evidence of remote hemorrhage, even if minimal in amount. The presence of fibroid necrosis and Charcot-Bouchard microaneurysms should be described (realizing, however, that these are nonspecific complications of microvascular disease).

Ideal Data Set

Special stains such as Masson trichrome, elastica van Gieson, and Movat pentachrome should be used in conjunction with immunohistochemistry (eg, for smooth-muscle α-actin, collagen types, etc) to provide a more illuminating picture of cerebral microvascular (arteriosclerotic) disease. The sclerotic index (SI=1−[internal diameter/outer diameter]),[98,99] an approximate measure of arterial/arteriolar stenosis, may be calculated for at least a subset of microvessels.

3. Microvascular Disease: CAA

Minimal Data Set

CAA can be evaluated quite accurately on hematoxylin/eosin–stained sections. Optimally, however, Congo red or thioflavin stains and amyloid-β immunocytochemistry would be used to assess the extent and severity of this angiopathy. Key assessments should include focal versus widespread, meningeal versus cortical, and arteriolar versus capillary (or both) involvement of the meningocortical microvasculature. Quantification of CAA severity can be roughly approximated by evaluating the degree of involvement of individual arterial walls (Vonsattel grading[99,100]), and multiplying by numbers of affected arteries per tissue section. Evidence of perivascular hemorrhage around affected arteries should be recorded, whether old (hemosiderin, hematoidin) or recent, as should the presence of CAA-associated inflammation (usually granulomatous) and other CAA-associated microangiopathies,[100] including microaneurysm formation, fibroid necrosis, etc.

Ideal Data Set

For more rigorous quantification of CAA extent/severity than that described above, grid-counting techniques in conjunction with amyloid-β immunohistochemistry are being developed (M.P. Frosch, personal communication, 2005).

4. Miscellaneous Microangiopathies

CAA and arteriosclerosis (lipohyalinosis) dwarf all other forms of cerebral microvascular disease in terms of their clinical importance. However, neuropathologists must also be vigilant for other types of disease, while realizing that these rarely present with dementia. These disorders include vasculitides (non-CAA associated), disseminated intravascular lymphoma, thrombotic thrmbocytopenic purpura, etc. Vigilance must be maintained for new or previously poorly characterized familial ischemic vascular dementia syndromes similar to cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), and hereditary endotheliopathy retinopathy nephropathy and stroke (HERNS).[101]

5. Parenchymal Abnormalities Associated With Cerebrovascular Disease

As a general rule, all infarcts must be assessed and recorded in terms of their number, size, location and estimated age. Acute lesions are less likely to be of importance in chronically evolving cognitive impairment, though they are obvi-

ously a marker of the duration and severity of cerebrovascular disease.

Minimal Data Set

Cystic lesions should be assessed as being large (arbitrarily >1 cm in maximal dimension), small (<1 cm), or microinfarcts (by definition not visible to the naked eye but detected on histologic sections). The term "lacunar infarct" should be reserved for cystic lesions that are smaller than 1 cm in size and located in the basal ganglia, brain stem or deep white matter (but *not* the cerebral cortex). Laminar necrosis is a distinct ischemic lesion usually associated with severe anoxic-ischemic encephalopathy or hypotension. Watershed infarcts, often symmetrical in the 2 cerebral hemispheres (and frequently in the anterior cerebral artery/middle cerebral artery watershed territory), should be noted. Assessment and significance of hippocampal injury, whether multifocal, segmental or multisegmental, or diffuse, is discussed below. Cribriform change is understood by most neuropathologists to represent (noninfarctive) enlargement of perivascular spaces. This change is questionably associated with cerebrovascular disease but should nevertheless be recorded, as should its location, whether in white matter or cerebral gray matter.

A major hemorrhagic component in an ischemic lesion suggests significant extravasation of blood into an infarct, or reabsorbed parenchymal hemorrhage. CAA may be associated with large or small bleeds (the latter sometimes visible only with microscopy) that are either preagonal or old. Such hemorrhages should be assessed in terms of number, age and estimated size, and an attempt made to link them to vascular disease present in the same brain specimen.

6. Leukoencephalopathy

It is deemed important to record minimally whether the anterior versus posterior white matter (or both), and periventricular versus deep white matter (or both) are affected. Optimally, these assessments should be made in myelin-stained sections (Luxol Fast Blue, Kluver-Barrera). A semiquantitative evaluation of "myelin loss" or, more accurately, "loss of myelinated tissue" (making no a priori judgment as to whether myelin pallor results from myelin or axon loss) can be made using an internal control such as the middle cerebellar peduncle on a semiquantitative scale of 0 to 3. Record should be made of whether the change is diffuse or multifocal.

Ideal Data Set

Quantitative assessment of large (grossly visible) infarct size, number, and location should be made. If possible, this should be done by taking digital images of brain slices and maintaining these in an easily searchable archive. Similarly, the topography of microinfarcts should be recorded, together with a quantitative assessment of their density in given locations. It may also be possible to coregister infarcts discovered at autopsy with antemortem neuroimaging data. The value of postmortem imaging (eg, of brain slices) is somewhat controversial because some MRI sequences are not interpretable in this material. Postmortem imaging may have value for assessing cortical thickness and "regularity", which can in turn be a surrogate marker for cortical scarring that results from microinfarcts. For optimal investigation of white matter lesions, immunohistochemistry could be employed using primary antibodies to myelin oligodendrocyte glycoprotein, phosphorylated neurofilament, glial markers, ubiquitin and amyloid precursor protein (APP).

7. Hippocampal Lesions

Given the importance of hippocampal structures in memory storage and retrieval, the hippocampus merits attention out of proportion to its size relative to the neocortex and subcortical white matter. It is also known to be a structure that frequently shows anoxic-ischemic change in the brains of elderly individuals.[102]

Minimal Data Set

Both the anterior and posterior hippocampus and the amygdala should be assessed. The presence of focal microinfarcts/scars versus diffuse or segmental (CA1, prosubiculum) neuron loss and astrocytic gliosis should be assessed. Note that patchy neuron loss and gliosis in a heavily "Alzheimerized" brain may be difficult or impossible to distinguish from anoxic-ischemic change. Hippocampal injury resembling hippocampal sclerosis is now reported in autopsy brain specimens from individuals with fronto-temporal dementia, especially the variant associated with motor neuron disease.[103,104] Hippocampal sclerosis latter can be fairly easily distinguished from anoxic-ischemic hippocampal injury by the judicious use of ubiquitin immunohistochemistry.

Ideal Data Set

Serial blocks of the hippocampus and quantitative assessment of neuronal loss and astrogloisis should be carried out; however, this may be feasible only in dedicated research laboratories.[105]

8. Incomplete Ischemic Injury

This entity, though suspected to be of importance clinically, does not have a widely appreciated or uniformly agreed on morphoanatomic correlate.[94] It may manifest as tissue rarefaction, which can be assessed by routine hematoxylin/eosin–stained tissue sections. Immunohistochemistry using antibodies which detect injury response (such as microgliosis, astrocytosis, or the presence of other "reactive" cells or surrogate markers of dendritic, synaptic or axonal damage) may, if assessed quantitatively, yield clues to subinfarctive brain injury. In this regard, morphological changes of reactive cells (for example, numbers of ramified processes in microglia), may be more important to assess than the number or density of these cell types. It will be important to establish correlations between these parameters and neuroimaging data. Purkinje cells of the cerebellum are important to examine in a given case of suspected hypoxic-ischemic encephalopathy, simply because of their vulnerability to this type of insult.

9. Mixed Vascular and Parenchymal Pathology

Cerebrovascular disease and AD pathology frequently coexist in the brains of elderly individuals.[106] The presence and degree of pathology related not only to AD but also to Lewy Body Disease and other types of dementing illness should be

carefully documented, so that the extent of comorbidity may be accurately assessed in a given brain specimen. These assessments can be made using standard criteria enunciated by NACC, CERAD, and others.[97] It is recommended that Braak staging be provided on all cases. In an effort to further assess the extent of AD pathology, amyloid-β (Aβ) burden staging.

What Information Should the Neuropathologist Provide?

In the final autopsy report the neuropathologist has the option of providing (1) a final list of diagnoses, reflecting her/his assessment of the relative significance of different types of structural abnormality in the central nervous system (CNS) and their relative contributions to a neurodegenerative illness, or (2) an unbiased summary of the parenchymal and vascular pathology present in a given case, leaving subsequent interpretation of the findings to others. It may be useful to calculate an all-encompassing "score" to estimate the degree of vascular pathology present in these cases; this is being attempted by some groups.[94]

The recommendations for obtaining essential information above are summarized in Table 8.

Experimental Models

The relationship between vascular dysfunction, brain injury, and cognitive changes (eg, VCI) in humans is only partly understood. Animals can be useful for modeling specific forms of vascular dysfunction that may lead to brain dysfunction, damage, and VCI. Animal models can potentially provide insight into how specific molecules, cells, and systemic conditions participate in vascular and parenchymal injury. Such models can also assist in defining targets for therapy. Finally, animal models can be used to perform preclinical assessment of new therapies to help guide human trials, as well as to develop biomarkers. In this section, we highlight some of the key issues surrounding the use of currently available animal models to study VCI, and provide recommendations for future research and model development.

Questions Addressed

1. What Animal Models Do We Currently Have to Understand the Pathophysiology of VCI?

A handful of experimental models are available to study VCI; however, these are not nearly as developed as those used to study acute ischemic brain injury or AD. This lack partly reflects the current lack of clarity in the definition of the clinical phenotype of this condition in humans, as well as the multitude of pathogenic pathways that can lead to the phenotype of VCI. Genetic and other risk factors can have a profound effect on the expression of vascular causes for cognitive impairment and on brain responses to vascular disease. These issues need to be further studied in virtually all the models listed below. In addition, the mechanisms by which vascular pathologies impair brain function leading to cognitive deficits in these models are poorly understood and need to be further studied.

Current models that provide insight into VCI include those in rodents and primates. Mice are attractive because of the ability to manipulate specific genes and to perform more detailed mechanistic studies. Primate models have been less fully used, but offer important advantages as well. These include the fact that nonhuman primate brains, like those of humans, possess large amounts of white matter; this feature seems particularly important given observed correlations between white matter injury and cognitive dysfunction in humans. In addition, disease states in primate models provide more direct functional and anatomic analogy to human cerebral diseases. In the aged primate, amyloid-β (Aβ) deposition in the microvasculature and in plaques analogous to similar to those seen in AD have been described. Well-described models of vascular injury, very relevant for studying the evolution and consequences of focal ischemia and chronic cerebral injury in humans, have been developed and can inform work in smaller animal systems. An additional advantage of nonhuman primates is the possibility to examine the chronic neurobehavioural consequences of cerebrovascular disease in subjects whose higher cognitive functions and behavior more closely model those of humans.

CAA

Models Available: (1) Transgenic mice over-expressing mutant forms of human APP that lead to AD, eg, APPsw.[107,108] These mice over-produce wild-type human Aβ and develop parenchymal plaques and CAA. (2) Transgenic mice expressing mutant forms of human APP that lead to familial CAA, eg, APPDutch, APPDutch/Iowa.[109,110] These mice produce mutant Aβ. (3) Squirrel, rhesus, marmosets, and others. These primate species are known to develop age-dependent CAA and parenchymal plaques.[111,112,123]

Pros. Rodent models exhibit pathology similar to that seen in human disease, including hemorrhages, Aβ, inflammation around amyloid, smooth-muscle and pericyte degeneration, basement membrane alterations, and concentration of pathology around leptomeningeal and penetrating arteries. Aged primate subjects show age-related accumulation of Aβ deposits, accumulation of parenchymal pathology, vascular alterations, and cognitive impairment (but these changes have only been studied in a select genus species subgroup).

Cons. Concomitant over-expression of APP in some transgenic models does not occur in humans, and the presence of mutant Aβ in Dutch or Dutch/Iowa mutants does not occur in most individuals with CAA. In addition, there is no strong evidence yet for the presence of infarcts that are associated with CAA in humans, although this issue has not yet been fully explored.

Future Directions/Recommendations. The development of more models in which there is selective vascular CAA without parenchymal plaques would be useful to the field. Also, animals that develop CAA in an anatomical distribution even more closely resembling that seen in human conditions would also be useful.

CADASIL

Models Available. Transgenic mice expressing Notch3 mutations at R90C[113] or R133C (Martin Dichgans, unpublished data, 2006) have been produced.

TABLE 8. Neuropathological Features of VCI Minimal Dataset to Be Collected

Cerebrovascular injury
• Is it ischemic or hemorrhagic?
• Is the hemorrhagic lesion(s) a major component?
Atherosclerosis (basal, peripheral or menigeal):
• Comment on: (1) severity of basal atherosclerosis (+ photograph); (2) anterior vs posterior circle of Willis; (3) left vs right; (4) dolichoectasia e.g. fusiform aneurysm present or absent and severity; (5) stenosis of major arteries (0–25%, 26%–50%, etc); (6) presence or absence of atherosclerosis in distal (meningeal) arteries.
• Assessment methods: histologic sections (representative) of major arteries
Microvascular disease (small vessel disease)
• Determine: (1) severity by semiquantitative methods (eg, using templates); (2) degree of inflammation (lymphocytes, macrophages; non-infarct-related); (3) presence of perivascular hemosiderin (evidence of remote hemorrhage); (4) presence of fibrinoid necrosis or Charcot-Bouchard microaneurysm(s)
• Assessment of arteries more important than veins. Areas to sample would be the CERAD plus anterior and posterior white matter. Thus sections from periventricular and deep regions, middle and anterior cerebral artery watershed zones bilaterally. This is also adequate to screen for CAA
Microvascular disease (CAA)
• Determine: (1) whether focal vs widespread, meningeal vs cortical, arteriolar vs capillary; (2) and quantify individual vessel severity, eg, X No. of arteries affected/section; (3) evidence of perivascular hemorrhage (old—hemosiderin); (4) CAA-associated inflammation and other CAA-associated microangiopathies (eg, microaneurysm formation or fibrinoid necrosis).
• Assessment methods: H&E stain but optimally Congo red/Thioflavin, Aβ immunocytochemistry to describe features such as perivascular neurites.
Other microangiopathies
• Is it vasculitides (non-CAA associated), intravascular lymphoma, TTP, etc?
• Is it any of the familial small vessel diseases such as CADASIL, CRV, HERNS?
Parenchymal abnormalities (Infarction)
• Determine: (1) in general infarct No., size, location, age of lesion (acute lesions likely unimportant except as marker of CVD); (2) large or small cystic; (3) borderzone/watershed (also assess microinfarcts); (4) lacunar (deep grey matter, brainstem, WM); (5) microscopic (ie, not visible grossly); (6) laminar necrosis; (7) hippocampal injury (focal, multisegmental, diffuse); (8) cribriform change (etat cribre) and location (deep white matter, subcortical structures CGM)
Major hemorrhagic component
• Determine: (1) resorbed large parenchymal hemorrhage(s); (2) large or small hemorrhages (eg, with CAA); (3) large infarcts with significant hemorrhagic component
Leukoencephalopathy
• Determine: (1) periventricular vs deep white matter; (2) anterior vs posterior deep white matter
• Assessment: myelin-stained sections (LFB, K-B), using an internal control, e.g. middle cerebellar peduncle. Also determine degree on a semiquantitative scale (0–3+) and diffuse or multifocal
Hippocampal lesions
• Determine:(1) focal microinfarct(s)/scars vs diffuse or segmental (CA1, prosubiculum); (2) neuron loss & astrogliosis—spectrum of injury in an attempt to distinguish from severe AD; (3)vascular vs degenerative anatomic features.
• Assessment: both anterior and posterior hippocampus and amygdale. More lesional burden derived from antiubiquitin sections.
Subinfarctive or incomplete ischemic injury
• Determine: (1) degree of rarefaction; (2) degree of gliosis both astrogliosis and microgliosis; (3) neuronal abnormalities (pyknosis) in cortex vs cerebellum (Purkinje cells)
• Assessment: Immunohistochemistry using primary antibodies that reflect injury. For example, microglia, astrocytes, synaptic and dendritic markers.
Mixed vascular-parenchymal (neurodegenerative) pathology
• Determine: (1) degree of pathologies associated with AD, LBD, other dementias.
• Assessment: use NACC, CERAD and other guidelines to determine type with vascular.
Final diagnoses
Provide: (1) Summary of parenchymal and vascular pathology; (2) Final list of diagnoses.

CRV indicates cerebroretinal vasculopathy; LBD, Lewy body disease; WM, white matter.

Pros. Mice develop similar vascular pathology and vascular reactivity problems similar to that seen in human disease.[113–115]

Cons. The mice do not exhibit ischemic lesions. The small amount of white matter in rodents limits comparison to humans, in which there is extensive white matter damage.

Future Directions/Recommendations. Detailed behavioral testing in these models needs to be performed. Studies in brain slices examining white matter function and susceptibility to injury may be informative.

Chronic Oligemia Models

Model. Bilateral carotid ligation in rats and baboons leads to sustained reduction in forebrain blood flow (oligemia) and white matter changes.[116–118]

Pros. White matter changes and cognitive impairment are seen.

Cons. This paradigm is technically more difficult to implement in mice, so that it is not as easy to assess the effects of genetic manipulation.

Future Directions. Bilateral carotid coiling may provide another useful model in mice. We also need to develop other models, in both mice and primates, with chronic reduction in cerebral blood flow.

Hypertensive Vasculopathy

Models. (1) Spontaneously hypertensive, stroke-prone rats (SHR-SP). These rats develop spontaneous hemorrhages and ischemic lesions when fed a Western diet with salt.[119,120] (2) Mice over-expressing genes of the renin-angiotensin system (*R*+/A+). When given the nitric oxide synthase (NOS) inhibitor N^G-nitro-L-arginine methyl ester (L-NAME) and fed a high salt diet, these mice develop microhemorrhages in the brain stem and other regions that show pathology similar to that of humans.[121] (3) Coarctation of the thoracic aorta in primates. This procedure produces gray and white matter lesions[122]

Pros. SHR-SP rats: Spontaneously occurring lesions in brain areas relevant to humans, as well as the presence of hemorrhagic and ischemic pathology, are useful features of this model. *R*+/A+ mice treated with NOS inhibitors and diet: Spontaneous hemorrhages in locations relevant to human disease are a positive feature. Coarctation of thoracic aorta in primates: This model has potentially more relevance to hypertensive white matter injury seen in humans, but cognitive testing has not been performed.

Cons. SHR-SP rats: Rats are not as amenable to genetic studies as mice. The genes and cellular mechanisms responsible for hypertension and stroke in these rats are unknown, and there is unpredictable timing of lesions. *R*+/A+ mice treated with NOS inhibitors and diet: This model needs further validation, the lesions are small, and multiple manipulations are required so that mechanistic studies may be difficult. Also, this mouse is already a double transgenic and further genetic manipulations may be challenging.

Future Directions/Recommendations. Behavioral studies in these models will be useful. Further validation and development of rodent and primate models of hypertensive vasculopathy are needed. Cerebrovascular and behavioral evaluation of existing primate models of hypertension may be informative. Coarctation of the aorta and other models of hypertension in primates need further exploration.

Aging Models

Models. In many species, aging is accompanied by architectural and functional alterations in brain vessels and parenchyma, targeting structures of the white and gray matter. One example of this process that occurs in certain mammalian species (eg, dogs, primates, humans) is amyloid deposition in the brain and cerebral arterioles. Diffuse and neuritic Aβ-containing plaques occur in the brains of aging mouse lemur, rhesus monkey, vervet monkey, and squirrel monkey, while both rhesus and squirrel monkeys develop CAA.[123] All are suitable models for studying the relationship of cognitive alterations to amyloid deposition in VCI. In rodents, senescence-accelerated mice (SAMP-8 mice) have evidence of accelerated aging, including apparent damage to brain vascular endothelial cells in the periventricular white matter and an abnormal blood-brain barrier.[124] Rat and mouse models of aging may also be useful, particularly genetically altered models which exhibit accelerated aging, vascular dysfunction and cognitive impairment.

Pros. Amyloid plaques seen in certain primate species with aging are very similar to human AD-like amyloid lesions. The large size of these animals allows for efficient handling for clinically related studies. Primates also have a large amount of white matter.

Cons. Rodents have little white matter.

Future Directions/Recommendations. Further studies of age-related changes in amyloid deposition in both the brain parenchyma and in blood vessels in species that develop these changes during the normal process of aging is recommended. Also, studies of the impact of these changes on function of the neurovascular unit and VCI would be useful.

Ex Vivo Models

Models. White matter damage is a prominent feature of VCI in humans. However, white matter injury is difficult to study in small animal models that have a low white-to-gray matter ratio. Thus, ex vivo preparations such as acutely isolated optic nerve, corpus callosum slice, and acutely isolated dorsal column are powerful and well-established models to study mechanisms of white matter injury.[125,126] Such studies will also allow one to further analyze the ionic and molecular details of cellular injury in white matter. This approach can be easily adapted to detect changes in the intrinsic vulnerability of white matter that may be conferred by specific genetic manipulations, risk factors, etc.

Blood vessels isolated from patient material could provide the opportunity to test hypotheses generated in animal models and in humans.

Pros. Examination of intrinsic properties of neural and vasculature elements in isolation could provide important insights into the cellular mechanisms underlying VCI.

Cons. The conclusions that could be drawn using isolated white matter preparations would be limited by the loss of normal connectivity and lack of interactions with vascular factors which may play a role in VCI.

Future Directions/Recommendations. Further studies with ex vivo preparations, including slices of different CNS white matter regions, are recommended to gain new insights into the cellular mechanisms underlying white matter damage and its contribution to VCI.

2. Cognitive Tests Used in Animal Models That Might Be Most Relevant to VCI

To control for the possible effect of systemic factors on cognitive function, it is critical to perform a battery of tests in each model that include a general physical examination and a basic neurological examination. A standardized battery of tests should be developed to assess sensory/motor function, learning and memory, and social and emotional functions. Water- and land-based learning and memory tests may both be useful. It is important not to equate each behavioral test with a specific human correlate. For appropriate testing in mice, please see the book by Crawley.[127]

For primates, examples of tests that could be used include the concurrent object discrimination task, visual spatial paired associates learning,[128] spatial memory, executive function tests, and motivational scoring.

3. What Are Some of the General Principles That We Can Learn From Animal Models?

Animal models provide a unique opportunity to examine the roles of individual risk factors in the development of VCI, including specific genes and chronic disease conditions such as hypertension or diabetes. Because these factors can be individually manipulated in animal models, one can assess their impact either alone or in combination, as well as potential synergistic interactions among them. A key step in this regard would be to generate rodent lines expressing both vascular and AD risk factors (for examine by crossing Notch 3 and APP mutants), as such lines might most closely model the combined vascular and AD pathology that seems to prevail in humans. Such models could be used, for example, to learn more about the fundamental mechanisms which underlie cellular injury in white matter, and to explore the regional differences that appear to exist in the intrinsic vulnerability of white matter to ischemic injury.

Animal models also have great power for translational research. They can be used for the development of new biomarkers; imaging techniques, as well as potentially unbiased genomic and proteomic techniques are important areas to explore in this regard. Finally, these models can be used for preclinical testing of potential new therapies.

Biomarkers

Diagnosis of VCI could be improved with the availability of a biomarker in either the blood or the cerebrospinal fluid (CSF) that would accurately separate cognitive impairment of vascular origin from AD.[129] This goal has been hampered by the heterogeneous nature of VCI and the prevalence of vascular components in patients with predominant features of AD. A number of markers have been found that provide both positive and negative information.[130] Studies in the CSF have been more successful than those in the blood in separating the various forms of cognitive impairment. Candidate markers in the CSF include (1) the serum albumin ratio, which can be used to identify blood-brain barrier damage to the small intracerebral vessels, (2) sulfatide, to identify demyelination of the white matter, (3) neurofilament, to identify axonal degeneration, and (4) matrix metalloproteinases (MMPs), to identify changes in the extracellular matrix associated with vascular disease. Although these markers are not specific to VCI, they can be used separately or in combination to increase diagnostic certainty. On the negative side, elevated levels of CSF tau and phospho-tau proteins are not found in VCI patients, but have been used to identify patients with AD.[130]

Blood-Brain Barrier in VCI

One marker that can be used as evidence for a disruption of the blood-brain barrier (BBB) is the albumin index in the CSF. In VCI patients, increased amounts of albumin appear in the CSF, suggesting leakage of the albumin, which is made in the liver, across a compromised BBB.[131,132] A compromised BBB is particularly obvious in patients with subcortical ischemic vascular dementia (SIVD).[133] The albumin in the CSF is clearly derived from the blood. However, attempts to show abnormalities in the BBB, using gadolinium–diethylenetriaminepentaacetic acid, were not successful in one small preliminary study.[134] In this small study, the types of VCD patients studied were not specified. On the other hand, another study found increased contrast-enhancement in diabetic patients, particularly in the patients with white matter hyperintensities on MRI; this study led the investigators to hypothesize that BBB disruption was occurring in VCI.[135] Thus, although the finding of increased albumin in VCI patients is well-established, further study is needed on the role of the BBB in the albumin flux.

Sulfatide

Sulfatide is a glycosphingolipid that accumulates in myelin. It is perceived to be a marker for ongoing demyelinization. Two studies have noted elevated levels of sulfatide in the spinal fluid of patients with SIVD.[136,137]

Neurofilament

Neurofilament is a cytoskeletal component that is concentrated in large myelinated axons. Neurofilament consists of 3 different proteins with different molecular weights, and it has been possible to measure neurofilament light subunit (NFL) in CSF. A greatly increased concentration of CSF- NFL has been measured in patients with SIVD,[138] and the increase was associated with the presence of white matter changes.[138] In patients with pure AD, without signs of vascular disease, CSF–NFL was found to be normal. These findings suggest that the increase in NFL among patients with SIVD does not reflect AD pathology, but rather the axonal damage that is characteristic of VCI.

Metalloproteases

MMPs have been identified in animal and human brain tissues in neuroinflammatory conditions, including cerebrovascular diseases.[139] These enzymes disrupt the basal lamina and tight junctions in blood vessels, causing opening of the BBB. MMPs attack myelin, making them a possible contributor to demyelination that occurs in SIVD or Binswanger disease. The source of the MMPs detected in the CSF is controversial. MMPs are produced by circulating white blood cells, including neutrophils and lymphocytes, which invade the brain during inflammation. However, they are also produced in most brain cells. Indexing the levels of MMP-9 in the CSF to those in the plasma, using albumin in both compartments as a reference, showed that the MMP-9 in multiple sclerosis was formed in the brain.[140]

Elevated levels of MMPs in the CSF are found in patients with VCI, but not in those with AD, suggesting that MMPs may be a surrogate marker for vascular disease in these conditions.[140] Autopsy studies have shown that MMPs are increased in brain cells of patients with VCI.[141]

Recommendations for Practitioners

Currently, CSF Albumin Index is the only clinically available test. It is generally elevated in VCD, but is a nonspecific finding with overlap with AD. There are no biomarkers in the blood. Tau and phospho-tau are negative markers that are elevated in the CSF in AD, but not in VCI.

Recommendations for Researchers

Several of the substances that show promise for aiding the diagnosis of VCI include sulfatide and neurofilament, which indicate white matter damage, and MMPs which are an indicator of vascular disease with inflammation.

As the accuracy of diagnosis improves and subgroup classification is agreed on, validation of these tests will be possible. Separation of the patients with AD from those with VCI can be done with improvements in diagnosis of AD. Patients with both AD and CVD, which are a large and growing group of patients, will remain a challenge.

It will be essential to combine advances in the various areas discussed in the NIH Workshop to reach diagnostic consensus. Ideally, the CSF studies, which are performed at the onset of the illness, will be validated by long-term follow-up, enabling them to be used in early diagnosis. Such an approach will ultimately allow for more focused therapeutic trials.

Genetics

Genetic research relevant to VCI has so far focused mainly on stroke and intermediate phenotypes for stroke, such as MRI white matter hyperintensities and carotid artery disease. Studies on VCI per se are scarce. As was pointed out in a recent review,[142] genetic determinants of VCI may include both genes implicated in vascular disease conditions that are known to be associated with stroke and cognitive impairment (eg, hypertension and carotid artery disease), and genes that affect the response of the brain to vascular disease (eg, genes impacting ischemic tolerance, neuronal plasticity, etc) Potential strategies for identifying genes of the second class were outlined in that review. The discussion below will focus on more general issues relevant to the search for both classes of genes.

Monogenic Disorders Associated With VCI

Several monogenic disorders with known genetic defects are associated with VCI. For example, VCI has been recognized as a clinically important problem in the following conditions (associated genes are listed in brackets): CADASIL (*NOTCH 3*), hereditary variants of CAA (*APP, CYSTATIN C*, and other genes), sickle-cell disease (*HBB* and other hemoglobin genes), Fabry disease (*GLA*), homocystinuria (*CBS* and other genes). These monogenic disorders may be useful for studying VCI because they provide patient cohorts sharing a common vascular pathology, thus eliminating some of the heterogeneity in disease etiology that is found in the general population.

VCI is also part of the phenotypic spectrum of several rare angiopathies with apparent autosomal dominant or recessive inheritance in which specific gene mutations have not yet been discovered. These include CARASIL, cerebroretinal vasculopathy, and HERNS. In some of these disorders the genes have been mapped to specific chromosomal regions, but the underlying genetic defects have yet to be identified. Their discovery will add to our understanding of pathogenic mechanisms leading to VCI.

Genetic Risk Factors for VCI

Genetic risk factors for VCI may be identified by linkage analysis or association studies. The general principles underlying these approaches and the methodological issues surrounding association studies in stroke have been covered by recent reviews.[142–144] Studies on genetic risk factors for VCI face specific challenges. Key issues include:

Definition of Target Phenotypes. Ideally, the phenotype should be:

1. Biologically meaningful
2. Quantitative
3. Easy to obtain
4. Possible to obtain in population-based studies.

It should further have considerable variation in the population under investigation. Clearly, cognition and the ability to carry out activities of daily living are ultimately the phenotypes of interest in VCI, and possible measures for those are suggested in the Clinical/Epidemiology and Neuropsychology sections of this article. However, rather than using cognitive or functional impairment as the target phenotype, genetic studies may focus instead on intermediate phenotypes known to (1) reflect vascular disease, and (2) be associated with cognitive impairment. Examples of such phenotypes include white matter hyperintensities, retinal vascular changes, intracerebral hemorrhage (possibly including microhemorrhages)[145,146] and markers for Aβ in the CNS such as Pittsburgh Compound-B.

Protocols Used for Phenotypic Assessment

These should be validated and robust across different centers (see below). They should further enable studying a large number of subjects with a not unreasonable (or impractical) level of effort.

Selection of Appropriate Controls

A major source of spurious association findings is population stratification. Cases and controls should therefore be ethnically matched and derived from the same source population. Detailed phenotyping in controls allows selecting for "hypernormal" controls: for example, individuals with "excellent cognitive performance" or "no white matter lesions". However, it may be more efficient to limit the phenotyping protocol in controls to a few basic items. In addition, genetic association studies should if possible control for the impact of known risk factors for cognitive impairment, including *APOE* genotype.

Selection of Candidate Genes/Candidate Gene Regions

The selection of candidate genes and polymorphisms can be optimized by following a number of rules outlined in a recent review article.[147] Genome-wide association studies have become technically feasible but are still very expensive and require huge sample sizes.[148] Currently, genome-wide association studies in VCI are probably not realistic, but this situation may change as the technology moves on.

Replication in Independent Samples

Attempts should be made to confirm any new association finding in an independent cohort of patients and controls. There may be differences between populations regarding the

associated sequence variants and haplotypes as well as the strength of association. Nevertheless, replication in independent cohorts is essential.

Because of the complexity of the phenotype, genetic association studies in VCI require particularly large sample sizes (probably in the order of several thousand individuals) and thus collaborative efforts of multiple sites. Repositories for DNA and immortalized cell lines of well-phenotyped subjects need to be established (as has been done, for example, for stroke and Parkinson disease). Finally, attempts should be made to attach genetic substudies to large treatment trials in VCI.

Clinical Trials

Measures of cognitive function quantify some of the most important aspects of brain function. Despite this, cognitive measures generally have not been included in past clinical trials in cerebrovascular disease. Stroke trials, for example, have usually focused on motor function or ability to carry out the usual activities of daily living. It is very clear, though, that stroke can also have disabling effects on executive and other cognitive functions which decrease the quality of life. Furthermore, whereas cognitive function is not entirely independent from motor, sensory, and autonomic function, cognitive deficits can be severe when other impairments are only mild or moderate.

The lack of cognitive function outcomes in clinical trials has come not from lack of interest in these domains, but from the inability of experts to agree on what are adequate or appropriate tests. The proposals for 5-minute, 30-minute, and 60-minute cognitive test batteries laid out in the Neuropsychology Section, therefore, represent a major step forward for the field. If the clinical research community can agree to include these tests in their protocols, then there will be a common basis for comparison between different studies. In addition, one of the major discussions in the review of grant proposals being considered for funding has been the selection of which cognitive tests to use. Lacking a consensus on what is acceptable, and having doubts about particular tests being proposed, reviewers are sometimes reluctant to let an otherwise well-designed and important trial go forward. Hopefully, the research community will accept the proposed battery as a minimum acceptable standard. As experience is gained, the battery may be changed and refined by consensus based on actual data.

Cognitive function tests have 3 uses in clinical trials: (1) for testing subjects to determine eligibility for the trial, (2) as a primary or secondary outcome measure, and (3) for determining adverse effects. Because time and cost are major considerations in clinical trials, the ability to do complete neuropsychological testing is constrained. Many neuropsychologists speak of spending hours with subjects in order to do thorough testing. In clinical trials, there are only minutes available, usually 5 or 10 minutes at most. In addition, it may not be possible for the tests to be administered by neuropsychologists. Instead, clinical coordinators and nurses may have to be trained. The usual reliability may not be attainable and more variance in test results will have to be accounted for.

An alternative to the protocol approach that is detailed in the neuropsychology section is the administration of a single, highly sensitive test. In the clinical trial setting, this may allow the investigator a quick check on the potential for cognitive impairment. There are many measures of cognitive function that might be appropriate for use as a single test in clinical trials. Some of the most sensitive to a wide spectrum of brain functions are timed tests of executive function. These include the Trailmaking Test and Digit Symbol Substitution Test. Both of these tests are also embedded in the proposed neuropsychology protocols. If time is available, one of these timed tests could be combined with the 5-minute protocol, which emphasizes the memory domain. Although these tests, when used alone, are not specific to a single etiology, they are sensitive to small but meaningful changes that are related to many clinical syndromes. Herein lays their potential value for clinical trials.

Trailmaking Test[149]

This is a test of scanning, visuomotor tracking, divided attention and cognitive flexibility. It is quickly and easily administered. It is in the public domain and may be copied without penalty or cost.[150] The test is highly sensitive to the presence of cognitive impairment,[151] most likely because it is timed and it requires intact cognitive functions in a variety of domains, including visuoperception, psychomotor and executive functions. It is sensitive to a variety of cognitive compromising conditions, including coronary artery bypass,[152] traumatic brain injury[153,154] and Parkinson disease.[155] Rapp and Reischies[156] recently found that Trailmaking test scores, along with other tests of executive function, differentiated nondemented elderly adults who later developed AD from those who did not. In the realm of VCI, Trailmaking test scores were lower in hypertensive patients with confluent white matter patients than in hypertensives without confluence[157] and in patients with brain stem lacunar infarction.[158] Hochstenbach et al[159] found a relationship between poor Trails B performance and poor perceived quality of life in a sample of stroke patients in a rehabilitation setting. O'Sullivan et al[160] found the Trailmaking Test and the Digit Symbol Substitution Test (DSST) to successfully differentiate patients with cerebral small vessel disease from age and education matched controls.

DSST[45]

The DSST has consistently been found to be the Wechsler subtest that is most sensitive to brain damage.[150] It is sensitive to cognitive impairment that precedes dementia, and DSST scores fall rapidly as dementia progresses.[161,162] It has also been shown to be sensitive to improvements in hypertension[163] and to cognitive effects of aerobic exercise.[164] DSST scores were inversely related to white matter rating scores in elderly community members who participated in the CHS[165] and were sensitive to cerebral small vessel disease in a smaller clinical study.[160] In a recent study with the Atherosclerosis Risk in Communities (ARIC) cohort, low baseline DSST scores predicted incident cardiovascular disease, including strokes, in a sample of middle aged subjects with no

history of stroke or coronary heart disease at the time of the baseline cognitive assessment.[166]

It is important to note that although both the Trailmaking Test and the DSST are highly sensitive, neither of them can be used to discriminate VCI from AD or a variety of other conditions affecting cognition. Hence, these tests could not be used alone to determine patient eligibility for clinical trials in VCI, but rather would have to be combined with imaging and risk factor assessment.

Conclusions

Unlike most workshops, where the report constitutes the end, these recommendations represent a beginning. For practical reasons, most of the participants were from North America, and the recommended standards are based mainly on the literature in English. The workshop was unique in that it brought together individuals from multiple disciplines for a single task: developing common standards. Final recommendations were sometimes reached after extensive debate, at the workshop and subsequently among the authors. By necessity, the initial recommended standards represent expert opinion and are of course influenced by the individual expertise and experience of the experts involved. Hence, their publication is an open invitation for debate, study and validation. A process including validation studies in different settings, different languages and among different cultures need to be carried out, and periodic reassessments of the recommendations will be scheduled. Moreover, if standardized, well-defined categories for data gathering become widely used, they could form the basis for provisional criteria that could subsequently be tested, validated and refined. The definition of clinical phenotypes will provide inspiration for new experimental models more representative of human cerebrovascular conditions resulting in cognitive impairment and dementia.

Our knowledge of the complex interactions between vascular and degenerative factors is at that bewildering stage that follows discoveries but precedes true understanding. This document marks an early attempt to integrate and focus on a common approach. Given this, unavoidably the recommendations may have omissions, debatable emphases and perhaps even outright errors, which we encourage our readers to redress. “Truth emerges more readily from error than from confusion” (Sir Francis Bacon, circa 1609).

Appendix

This article is based on discussions at a workshop entitled “Vascular Cognitive Impairment: Harmonization Criteria” that was held by the National Institutes of Neurological Disorders and Stroke in Washington, DC, on April 24–27, 2005, and cosponsored by the Canadian Stroke Network, The Institute of Ageing, The Institute of Circulatory and Respiratory Health and The Institute of Neuroscience, Mental Health and Addiction of the Canadian Institutes of Health Research, the Alzheimer’s Association, and the NIH Office of Rare Diseases. Participants in the workshop were as follows:

Co-Chairs: Gabrielle G. Leblanc, PhD; Costantino Iadecola, MD; and Vladimir Hachinski, MD, DSc.

Working group co-chairs: Ron C. Petersen, MD, PhD; Monique M. Breteler, MD, PhD; David L. Nyenhuis, PhD; Sandra E. Black, MD; William J. Powers, MD; Charles DeCarli, MD; Raj N. Kalaria, PhD, FRCP; Harry V. Vinters, MD; David M. Holtzman, MD; Costantino Iadecola, MD.

Participants: Norman J. Beauchamp, MD, MHS; Richard T. Benson, MD, PhD; David Cechetto, PhD; Ray Chaudhuri, PhD, MBA; Christopher Chen, MD; Helena C. Chui, MD; Charles DeCarli, MD; Gregory J. del Zoppo, MD, MS; Dennis Dickson, MD; Emmeline Edwards, PhD; Timo Erkinjuntti, MD, PhD; Frank M. Faraci, PhD; Giovanni B. Frisoni, MD; Matthew P. Frosch, MD, PhD; Katrina Gwinn-Hardy, MD; John Hallenbeck, MD; Jonathan D. Horsford, PhD; George Howard, PhD; Miia Kivipelto, MD, PhD; Story C. Landis, PhD; Lenore J. Launer, PhD; David J. Libon, PhD; Oscar L. Lopez, MD; Hans O. Lüders, MD, PhD; Ann C. McKee, MD; Harold Merskey, DM, RFCP; James F. Meschia, MD; Claudia S. Moy, PhD; Truls Ostbye, MD, PhD; Leonardo Pantoni, MD, PhD; Giulio M. Pasinetti, MD, PhD; Creighton Phelps, PhD; Barbara Radziszewska, PhD, MPH; Bruce R. Ransom, MD, PhD; Gustavo C. Roman, MD; Jonathan Rosand, MD, MS; Ralph L. Sacco, MD, MS; Stephen Salloway, MD; Mary Sano, PhD; Ingmar Skoog, MD, PhD; Glenn E. Smith, PhD; Donald T. Stuss, PhD; William H. Thies, PhD; William Van Nostrand, PhD; Steven Warach, MD, PhD; Lon White, MD, MPH; Philip A. Wolf, MD; Katherine Woodbury-Harris, PhD; Chris Zarow, PhD.

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Disclosures

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