

Vascular dementia

Diagnostic criteria and supplementary exams

Recommendations of the Scientific Department of Cognitive Neurology and Aging of the Brazilian Academy of Neurology. Part I.

Elias Engelhardt¹, Carla Tocquer², Charles André³, Denise Madeira Moreira⁴, Ivan Hideyo Okamoto⁵, José Luiz de Sá Cavalcanti⁶ and Working Group on Alzheimer's Disease and Vascular Dementia of the Brazilian Academy of Neurology

Abstract – Vascular dementia (VaD) is the most prevalent form of secondary dementia and the second most common of all dementias. The present paper aims to define guidelines on the basic principles for treating patients with suspected VaD (and vascular cognitive impairment – no dementia) using an evidence-based, systematized approach. The knowledge used to define these guidelines was retrieved from searches of several databases (Medline, Scielo, Lilacs) containing scientific articles, systematic reviews, meta-analyses, largely published within the last 15 years or earlier when pertinent. Information retrieved and selected for relevance was used to analyze diagnostic criteria and to propose a diagnostic system encompassing diagnostic criteria, anamnesis, as well as supplementary and clinical exams (neuroimaging and laboratory). Wherever possible, instruments were selected that had versions previously adapted and validated for use in Brazil that take into account both schooling and age. This task led to proposed protocols for supplementary exams based on degree of priority, for application in clinical practice and research settings.

Key words: recommendations, vascular dementia, criteria, neuroimaging, laboratory exams.

Demência vascular: avaliação cognitiva, funcional e comportamental. Recomendações do Departamento Científico de Neurologia Cognitiva e do Envelhecimento da Academia Brasileira de Neurologia. Parte I.

Resumo – A demência vascular (DV) é a forma mais prevalente de demência secundária e segunda forma mais comum. O presente artigo visa definir recomendações dos princípios básicos para tratamento dos pacientes com suspeita de DV (e comprometimento cognitivo leve sem demência) usando uma abordagem sistematizada baseada em evidências. O conhecimento usado para definir estas recomendações foi recuperado de pesquisa de várias bases de dados (Medline, Scielo, Lilacs) contendo artigos científicos, revisões sistemáticas, meta-análises, publicados nos últimos 15 anos, ou antes, se pertinente. As informações recuperadas e selecionadas pela relevância foram usadas para analisar os critérios diagnósticos e propor um sistema diagnóstico incluindo critérios diagnósticos, anamnese, bem como exames complementares (neuroimagem e laboratório). Sempre que possível, os instrumentos foram selecionados com versões previamente adaptadas e validadas para uso no Brasil, segundo escolaridade e idade. Os protocolos propostos para exames complementares basearam-se no grau de prioridade, para aplicação na prática clínica ou em pesquisa.

Palavras-chave: recomendações, demência vascular, critérios, neuroimagem, exames laboratoriais.

¹Full Professor (retired) – UFRJ, Coordinator of the Cognitive Neurology and Behavior Sector, INDC, CDA/IPUB, UFRJ, Rio de Janeiro RJ, Brazil; ²Neurologist, Masters and PhD in Neuropsychology, Claude Bernard University, France; ³Associate Professor of Neurology, Faculty of Medicine, UFRJ, Medical Director of SINAPSE Rehabilitation and Neurophysiology, Rio de Janeiro RJ, Brazil; ⁴Adjunct Professor of Radiology, School of Medicine, UFRJ, Head of Radiology Sector, INDC, UFRJ, Rio de Janeiro RJ, Brazil; ⁵Department of Neurology Neurosurgery, UNIFESP, Institute of Memory, UNIFESP, São Paulo SP, Brazil; ⁶Adjunct Professor of Neurology, INDC, UFRJ, Cognitive Neurology and Behavior Sector, INDC, UFRJ, Rio de Janeiro RJ, Brazil.

Elias Engelhardt – Av. N.S. de Copacabana, 749/708 - 22050-002 Rio de Janeiro RJ - Brazil. E-mail: eliasz@centroin.com.br

Disclosure: The authors report no conflicts of interest.

Received September 3, 2011. Accepted in final form November 2, 2011.

Introduction

Vascular dementia (VaD) is characterized by cognitive impairment, functional decline, behavioral disorders and neurological symptoms secondary to cerebrovascular disease (CVD). Vascular cognitive impairment (VCI) includes from very mild forms of impairment (VCI no dementia [CIND] and vascular mild cognitive impairment [VMCI]) to more severe forms, including VaD and its clinical stages,¹⁻⁵ thus constituting a VCI/VaD spectrum. CVD can manifest associated with AD, constituting mixed forms such as AD+CVD and Mixed Dementia (MD).⁶⁻⁹ Pure forms of VCI/VaD associated with AD constitute vascular cognitive disorder (VCD),¹⁰ a concept later incorporated into VCI.¹¹

VaD (and likewise CIND) is a clinically and anatomically heterogeneous condition. The clinical characteristics of VaD differ to those of most neurodegenerative diseases, since the latter tend to typically present sequential and predictable progression according to the underlying pathology (e.g. AD [amnestic form]). This heterogeneity stems from pathophysiologic aspects such as:

- (i) The presence of ischemic (or hemorrhagic) intracerebral lesions (vascular ictus, cerebral vascular accident [CVA], cerebrovascular attack) with varying neuropathologic and neuroimaging characteristics. Ischemic ictus can be found in sites of large caliber arteries (single, multiple, strategic infarcts) and of lesions in regions nourished by small caliber arteries and arterioles (minor infarcts [which may be strategic], lesion in bordering areas, lacunes, white matter lesion). Hemorrhagic ictus can also cause similar pictures.¹²⁻¹⁵
- (ii) The relevance of site, size and number of lesions. Lesions must affect associative and/or limbic/paralimbic regions ("strategic areas")¹⁶ with initial symptoms and evolution varying accordingly. Thus, VaD can present a range of different neuropsychological patterns, with a predominance of executive dysfunction (mainly subcortical type), "scattered" impairments (due to multiple lesions) and impaired memory (hippocampal, median prosencephalic, and thalamic lesion) among others¹⁷. The size (volume) of infarct should be substantial (~100 cm³) in pure VaD and smaller (~50 cm³) in AD+CVD. The majority of patients with intermediate volume lesions (50 to 100 cm³) present with cognitive impairment.^{16,18-19} Infarcts smaller than the minimum stipulated volume can cause VaD, denoting the concept of "strategic site",¹⁹ later referred to as VaD due to "strategic infarct".²⁰

Detailed descriptions of classifications and characteristics of the main subtypes of VaD can be found in a number of published sources.^{13,15,21}

The goal of the working group involved in the module "Vascular Dementia: diagnostic criteria and supplementary exams" was to put forward basic guidelines based on evidence for diagnosing VaD. This is the first task of its kind undertaken on VaD in our milieu, having led to a preliminary publication of a version of these guidelines²².

The previously published version was revised and split into two parts:

- (i) diagnostic criteria and supplementary exams (part I).
- (ii) cognitive, functional and behavioral assessment (part II).

This first part of the diagnostic module for VaD covers diagnostic criteria and anamnesis, in addition to clinical and supplementary exams.

Methods

The guidelines (recommendations and suggestions) were based on publications retrieved from electronic databases (Medline, Scielo, Lilacs) and encompassed scientific articles, systematic reviews, meta-analyses, largely published within the last 15 years, or earlier when pertinent. Consensus and Studies on the theme or related subjects were also examined.^{11,23-31}

Classification of evidence and levels of recommendation

The scientific evidence for diagnostic assessment was evaluated according to pre-established levels of certainty (Classes I, II, III and IV) and recommendations were graded according to strength of evidence (*Level A, B or C*). Additionally, important clinical issues were addressed for which evidence is questionable (Practice Option) and, when no evidence was available, recommendations were made based on the experience and consensus of the task force under "Good Practice Point"^{32,25} (Table 1).

These guidelines may not be applicable under some circumstances and decisions on whether to apply recommendations must be taken in light of the individual clinical presentation of the case and of the resources available.³²

Diagnostic steps

The diagnostic steps outlined below should be followed systematically to determine the diagnosis of VaD as accurately as possible.

Diagnostic criteria

The diagnostic criteria for VaD include the official sets (CID-10-CDP³³ and DSM-IV³⁴) as well as those devised specifically for research (CADDTC,³⁵ NINDS-AIREN,³⁶ NINDS-AIREN modified).³⁷ Ischemic scores are also routinely used, the most common of which is the Hachinski (HIS).³⁸

These criteria are similar on several aspects while differ

Table 1. Classification of evidence for diagnostic measurement and levels of recommendation.^{32,25}

Classification of evidence	
Class I	Prospective study involving a broad spectrum of individuals with the suspected condition (using gold standard for defining cases), where test has been applied in blinded manner, enabling assessment of appropriate diagnostically accurate tests.
Class II	Prospective study involving a limited spectrum of individuals with the suspected condition, or well-planned retrospective study in broad spectrum of individuals with confirmed condition (using gold standard), compared with broad spectrum of control subjects, where test has been applied in blinded manner, and enables measurement of appropriate diagnostically accurate tests.
Class III	Retrospective study in limited spectrum of individuals with the confirmed condition and control subjects, in which tests have been applied in blinded manner.
Class IV	Any design methodology in which test has not been applied in blinded mode or is drawn from evidence based exclusively on opinion of a specialist or on a descriptive case series (without controls).
Levels of recommendation	
Level A [Standard]	Requires at least one convincing Class I study or at least two convincing Class II studies.
Level B [Norm]	Requires at least one convincing Class II study or indisputable Class III evidence.
Level C	Requires at least two convincing Class III studies.
Practice option	Requires Class IV evidence.
Good practice point	Based on the experience and consensus of the task force after considering important clinical questions for which no evidence (as per above) is available.

on others, such as the definition of dementia (the majority incorporate memory impairment of varying degrees), characterized by vascular lesions and evidence of deficit.¹³ Thus, classification of cases can differ depending on the criteria used, with sensitivity ranging from 32.5% to 91.6%. Therefore, the current criteria are not interchangeable, potentially identifying different patient groups labelled as VaD.³⁹⁻⁴¹ However, within their respective limits, all of the criteria are able to identify patients with VaD,^{39,40,42,43} and relatively successfully distinguish the disease from “pure” AD, and less effectively from MD. Concerning research or clinically-controlled trials, in which false positive cases should be excluded (generally AD+CVD), only highly specific criteria tend to be employed (such as NINDS-AIREN and CADDTC).^{39,44,40}

The diagnosis of subcortical VaD is challenging using current criteria. Memory impairment may not be an initial or marked symptom, where another cognitive domain (or more than one), such as executive dysfunction may be more severely affected. The proposed NINDS-AIREN modified for subcortical VaD⁴⁵ remedies this weakness by focusing on executive dysfunction and the presence of high grade subcortical ischemic lesions (leukoaraiosis, lacunes).^{37,46,47}

Class I cliniconeuropathological studies in possible and

probable VaD diagnosed by NINDS-AIREN have shown low sensitivity and high specificity for probable VaD (43%/95%),⁴⁸ and likewise for possible VaD (55%/84%) and probable VaD (20%/93%),⁴⁴ with similar aspects evident for the other criteria sets⁴⁴. The cited criteria are deemed to offer the best sensitivity/specificity profile.

The HIS is a clinical instrument with differentiated scores for AD, VaD (MID type) and MD.³⁸ A meta-analysis study with neuropathological correlation revealed sensitivity/specificity of 89%/89.3% for distinguishing between AD and VaD (MID), proving capable of correctly classifying 83.8% of patients with VaD (MID). This was found to be frequently elevated in patients diagnosed applying the NINDS-AIREN or CADDTC⁴⁹. The lack of cognitive and neuroimaging data render the HIS insufficient when used alone.^{42,43}

The key elements that emerge from these criteria constitute a diagnostic triad of VaD²¹.

Dementia syndrome

- With memory and/or executive function impairment.

Vascular cause

- Post-ictus or subcortical ischemia.

Adequate relationship

- Temporal [immediate, subacute, insidious].

- Functional [lesion to structures of cognitive integration].

Based on the diagnostic criteria, a general definition of VaD can be derived and, considering the variations presented, its simplified unification can be formulated as shown below. The basic characteristic of VaD is cognitive impairment of multiple domains, with compromise often being non-uniform. For VaD, memory impairment is a requisite (in most criteria) together with one or more of the following signs and symptoms: aphasia, apraxia, agnosia and executive dysfunction. Deficits of the disease must have a major impact on occupational or habitual activities and be marked by significant decline compared to previous level of functioning. The presence of neurological signs and symptoms is also a requirement, in addition to laboratory evidence or neuroimaging findings indicative of CVD, deemed to be etiologically related to the condition. The condition should not manifest exclusively during the course of delirium or major psychiatric disorder²¹.

Recommendations – A diagnosis of VaD must be based on specific criteria, with NINDS-AIREN being the most frequently used in research settings (*Level A*). The HIS can be recommended although with some restrictions, given a lack of cognitive and neuroimaging data (*Level C*). The diagnostic triad of VaD can represent a brief option for diagnosis (*Good Practice Point*).

Anamnesis

Anamnesis is fundamental and must include questions on all aspects related to a dementia condition of vascular cause, such as mode of onset, pattern of progression, prior history (CVA, revascularization), comorbidities (SAH, DL, DM, anemia, sleep and psychiatric disorders), habits (eating, life-style, tobacco and alcohol use), familial and educational history. Specific questions on cognition, activities of daily living and behavior are necessary. It is important to obtain a full list of drugs used and prescribed, as well as alternative medications.^{21,24,50,51}

Recommendations – Anamnesis is fundamental and data must be supplemented by a companion that is as well informed as possible (*Level A*).

Physical and neurological exams

A general physical exam can disclose frequent comorbidities, particularly in elderly patients, that can rapidly worsen cognitive, functional and behavioral status. These comorbidities or complications can include depression, cardiovascular disease, infections, dehydration, collateral effects of medications, delirium, falls, incontinence, anorexia and obesity. There is a strong correlation between

comorbidities and cognitive status in VaD (Class IV).⁵² Clinical neurovascular assessment (palpation, auscultation) is also part of a thorough exam (see “Vascular neuroimaging”). Neurological examination is necessary and the presence of neurological symptoms makes up part of the diagnostic criteria of VD^{51,53} (Class II).

Recommendations – All patients presenting with, or suspected of having dementia must be submitted to a general physical exam aimed at detecting comorbidities, in addition to a neurovascular exam (*Good Practice Point*), as well as a neurological exam (*Level B*).

Supplementary exams

Supplementary exams play a key role in the diagnostic process of VaD (and of vascular CIND). In this regard, neuroimaging is fundamental, particularly MR, and also laboratory exams on blood, and should be incorporated into the routine. Other exams can be performed according to the case being analysed⁵⁴, classified into obligatory, desirable and z, in line with specific diagnostic needs (Table 2).

Neuroimaging

Neuroimaging plays a pivotal role in the diagnostic process of patients with suspected dementia or that present with VaD (and vascular CIND), providing not only structural but also functional information.⁵⁴⁻⁵⁶

Table 2. Supplementary exams and indication hierarchy (see text for original references, translations and validations).

Supplementary exams
Structural neuroimaging ⁽¹⁾
• Cranium CT or MRI
• Hippocampus (visual assessment)(CT or MRI) ⁽²⁾
Vascular neuroimaging ⁽³⁾
• Duplex ultrasonography (carotids and vertebrals)
• CT-Angiography or MR-Angiography (intracranial and extracranial carotid and vertebral arteries [veins])
Functional neuroimaging ⁽³⁾
• Structural MRI (¹ H MRS)
• Perfusion (CT or MRI)
Isotopic neuroimaging ⁽³⁾
• SPECT or PET-CT/MRI
Clinical electrophysiology ⁽³⁾
• EEG
Laboratory exams (clinical pathology)
• Blood exam (routine, risk factors) ⁽¹⁾
• CSF Exam ⁽³⁾
• Genetic exam ⁽³⁾
• Others (enzymes, antibodies, biopsy) ⁽³⁾

⁽¹⁾obligatory; ⁽²⁾desirable; ⁽³⁾occasional.

Structural neuroimaging

This can be obtained through computed tomography scans (CT) or magnetic resonance imaging (MRI). Long considered merely for “excluding” brain lesions as the cause of dementia (e.g. tumors, hematomas, hydrocephaly), these techniques now exercise an important role of “including” diagnoses (e.g. neurodegenerative diseases, cerebrovascular diseases), through evidencing aspects considered characteristic of certain dementia types (e.g. hippocampal atrophy, as a marker of AD, or infarcts and lesions in white matter, as characteristics of VaD).⁵⁷⁻⁵⁹ It should be noted that despite confirmation of CVD on neuroimaging, the method cannot reliably diagnose VaD.⁶⁰ However, the absence of CVD on neuroimaging offers strong evidence against dementia of vascular etiology.⁶¹

MRI is the method of choice for reaching a diagnosis of VaD (and vascular CIND), given its high sensitivity and spatial resolution, and ability to provide a greater amount of reliable data. The preferred magnetic field intensity is 1.5T or greater,⁶² where 0.5T may be acceptable.

The basic sequences needed are diffusion (DWI), 3D-T1, T2, T2-FLAIR and GE-T2 (gradient echo).^{56,63-65} CT should be used when no MRI device is available and in special situations (pace-maker fitted, intracranial ferromagnetic metal clips, psychological grounds etc.).²² Both techniques, within the scope of their characteristics, are able to obtain information on anatomy and presence of vascular lesions (infarcts, lacunes, changes in white matter, hemorrhages) and other pathologies, providing information on quantitative (number and volume) and topographic (localization) aspects. Ischemic changes in white matter (hypodensities – hyperintensities)(leukoaraiosis) can be assessed using visual and automated scales.^{15,64-70} The presence of hippocampal atrophy can also be assessed (see “Hippocampal atrophy”).

Structural neuroimaging must be performed as routine and a number of diagnostic criteria for VaD expressly require neuroimaging as a core item^{71,56}, such as the NINDS-AIREN, in which the technique is essential for diagnosing probable VaD, where lack of the method leads to a default diagnosis of the “possible” category⁶. Moreover, the criteria specify which vascular territories are “relevant” for VaD. Use of NINDS-AIREN operating guidelines for classifying radiological aspects led to a significant increase in diagnostic reliability among professionals assessing images from 40% to 60% (Class II).

Hippocampal atrophy – The assessment of degree of atrophy can be carried out by CT or MRI (with the latter being more reliable) using the visual assessment volumetric measurements (manual or automated), with the latter deemed more accurate.⁷³⁻⁷⁶ Comparative studies have

shown good correlation among these techniques.^{77,78} Visual scales can be employed in clinical practice as well as clinical research, particularly in cross-sectional studies.^{76,79-81} T2-MRI or FLAIR can be used to distinguish the nature of the hippocampal atrophy. High signal, although also seen in AD, is not characteristic of this condition, being more often found in hippocampal sclerosis. On the other hand, ischemic changes in these regions can be better distinguished on FLAIR.⁸²

MRI studies have shown hippocampal atrophy through visual (VaD) or volumetric assessment (subcortical VaD), to a lesser degree compared to AD but to a greater extent than in normal controls, in cases of dementia with similar severity.⁸³⁻⁸⁶ The findings on neuroimaging were confirmed by neuropathological studies showing that hippocampal volume was lower in VaD than in normal controls, but greater compared with atrophy found in AD.⁸⁷⁻⁸⁹

Diffusion tensor – Diffusion tensor imaging (DTI) is a technique for assessing the integrity of white matter fibers using quantitative fractionated anisotropy (DTI-FA) and tractography (DTI-TR). DTI-FA is an important technique in considering the large extension of white matter, and has been previously applied in clinical practice.⁹⁰⁻⁹⁵ DTI-TR can visualize the bundles interconnecting various regions whose interruption can cause a range of different disconnection syndromes. The method is not routinely used in clinical practice.^{95,96}

Vascular neuroimaging

Neurovascular assessment entails, beyond clinical examination, duplex ultrasonography (USG) of the extracranial carotid and vertebral arteries and CT-angiography or MRI-angiography of intracranial and extracranial carotid and vertebral arteries (from their point of origin).^{97,98} USG tends to be the initial exam and enables visualization of the vascular wall, detecting atheromatous plaques and stenosis while also providing a measure of intima-media thickness of the carotids, an early marker for wall pathology and cardiovascular risk factor. The characteristics of blood flow can also be verified, constituting a functional aspect.⁹⁹ MRI-angiography and CT-angiography visualizes the entire cervical and intracranial tree (and venous system when necessary) and the vascular pathology present (atheromatous plaques, stenosis) which is related to flow and perfusion disorders with potential to cause brain lesions.⁹⁷⁻¹⁰²

Recommendations – Structural neuroimaging should be used in all patients with suspected dementia, preferably using MRI (*Level A*). In the impossibility of using MRI, CT can serve as an alternative method (*Level B*).

Hippocampal atrophy must be assessed in all patients with the aim of reaching a diagnosis of pure VaD or VaD associated to AD (*Level B*). Neurovascular assessment can be necessary for clinical clarification and determining therapeutical interventions (*Good Practice Point*).

Functional neuroimaging

Functional aspects of neuroimaging often provide useful supplementary information to the diagnosis, such as proton MR spectroscopy (^1H MRS), CT and MRI perfusion, besides isotopic techniques including Single Photon Emission Computed Tomography and Positron Emission Tomography (PET).

Proton spectroscopy – ^1H MRS represents biochemical information via MRI, which can be obtained at the same time as structural acquisitions. Studies in AD have shown changes in mI/Cr in the posterior region of the cingulate (PC)¹⁰³ and reduced Naa/Cr in hippocampi (HCs), with progressive decline according to stage of the disease.¹⁰⁴ In addition, comparing alterations in HCAs with those in PC for AD enables staging by spectroscopy.¹⁰⁵

Studies of these structures in VaD (HCs, PC) are scarce. Investigations have been performed mainly for PC, comparing findings in several different dementia types (AD, FTL, DLB) and subcortical VaD in mild stages, involving a small number of patients, and have revealed reduced Naa/Cr, although within one standard deviation of the normal group.⁶ Other studies however, found no significant difference in Naa/Cr ratio of PC between AD and VaD.¹⁰⁷ A study focusing on HCAs (and frontal and parietal lobes) in dementia without vascular lesions (AD) and with vascular lesions (lacunes)(subcortical VaD) showed a lower Naa/Cr ratio in HCAs among AD cases, whereas this ratio was similar in dementia patients with lacunes and in normal controls.¹⁰⁸ ^1H MRS can be used as a resource in diagnosing VaD, particularly as a differential item with AD and in suspected cases of AD+VaD (MD).⁶

Isotopic neuroimaging – SPECT and PET are used fairly frequently in diagnosing dementia. Some studies using SPECT were designed to compare AD with other types of dementia and have shown sensitivity and specificity for AD vs. VaD of 71% and 75%, respectively.¹⁰⁹ However, although results were variable, the techniques seems to be useful for distinguishing AD from VaD, but use for diagnostic purposes without previous structural imaging is not advised.¹¹⁰ PET can differentiate AD from VaD by disclosing temporo-parietal pattern of hypometabolism in AD, or predominant frontal lobe damage in VaD.¹¹¹ Different regional patterns of hypoperfusion as seen by SPECT, or hypometabolism seen on PET, can assist in differentiating diverse neurodegenerative types and VaD. Images on

SPECT and PET in VaD show diverse patterns according to VaD subtype – such as multifocal pattern seen in dementia due to multiple infarcts, or with a more diffuse pattern associated to extensive lesion of white matter and lacunes.⁵⁷

Recommendations – The use of ^1H MRS can be valuable for certain cases of VaD and for differentiating with MD (*Practice option*). SPECT and PET can be used in cases where there is diagnostic doubt after clinical work-up and structural imaging, but should not be used as a standalone imaging assessment (*Good Practice Point*).

Blood exam

The blood test is a necessary part of the assessment in cases of cognitive disorder so as to: (i) identify comorbidities and/or complications; (ii) reveal potential risk factors; (iii) explore causes of frequently associated confusional states, and (iv) less often, identify the primary cause of the dementia. Cognitive disorders can be associated to a broad array of metabolic, infectious, and toxic conditions which must be identified and treated.³⁰

Besides routine items (full blood count, ESR, electrolytes, glucose, renal and hepatic function tests, and TSH), items should be ordered that represent vascular risk factors (VRFs) which merit separate consideration in VCI/VaD. VRFs are intrinsically linked to CVD (and transient vascular ictus or report of ictus symptoms in its absence).¹¹² These are also associated to reports of ictus symptoms in the absence of diagnosed ictus or transient ischemic attack.^{113,114} VRFs are numerous and encompass metabolic, toxic, genetic, cardiovascular, and demographic factors, being divided into non-modifiable and modifiable (the majority) with this latter group being susceptible to preventive measures.^{12,31} A comprehensive study showed that among the numerous VRFs for cerebral vascular ictus, just 10 were associated to 90% of cases, namely: arterial hypertension, smoking, waist-hip ratio, high risk diet, moderate physical activity, diabetes mellitus, excessive alcohol intake, psychosocial stress and depression, cardiac causes and ratio of apolipoproteins B for A1 (Class I).¹¹⁵ It has been suggested that ≥ 3 VRFs among those cited place the brain at high risk of cognitive impairment.³⁰ Cognitive decline associated to VRFs in the absence of clinical ictus of dementia has also been observed, with theory proposing that subclinical CVD proves an important link among the main VRFs for ictus and cognitive function.¹¹⁷ Healthy elderly can present subclinical CVD,¹¹⁸ leading to the hypothesis that CVD, faster cerebral atrophy, abnormal cerebral white matter and clinically asymptomatic brain infarcts represent possible mechanism linking VRFs to risk of future ictus and cognitive dysfunction.¹¹⁹ Genetic risk factors are examined separately (see “Genetic exam”).

Recommendations – Blood tests should be performed at first assessment, including routine items and those representing a potential cause of cognitive impairment or as comorbidity, including exams which represent VRFs (*Level A*). More in-depth tests can be necessary in selected cases (*Good Practice Point*).

Other exams

This category includes exams performed in special situations according to specific indications.

Cerebrospinal fluid – The cerebrospinal fluid exam (CSF) has an important place in diagnosing neurodegenerative dementia (AD, FTD, DLB, CJD) through the study of markers based on β -amyloid peptide (β A) and total tau and phospho-tau protein.⁵⁴ Levels of A β 42 are reduced in AD (and in AD+CVD) and increased in VaD, enabling AD (and AD+CVD) to be discriminated from VaD. A β 42 has proved an important resource for discriminating AD vs. VaD and possibly improving the diagnostic precision of cases classified as MD (presence of CVD on neuroimaging). Tau protein is high in AD (and in AD+CVD) and low in VaD.¹²⁰⁻¹²² Levels of phospho-tau exhibit differentiated increase, being greater in AD, intermediate in AD+CVD and lower in VaD.^{122,123} Analysis correlating A β 42 and total tau have shown high specificity in AD and low specificity in VaD 48% [29-67]), possibly owing to the presence of neurodegenerative lesion in this condition.¹²⁰

Recommendations – The CSF exam is recommended in certain situations (inflammatory diseases, vasculitis, rapidly progressive dementia)(*Good Practice Point*). The markers based on tau protein and A β 42 can be used as a complement in cases with diagnostic doubt (*Level B*).

Electroencephalograph – EEG in cases of AD, AD+CVD (with pathological confirmation) and controls discloses abnormalities in the majority of patients from pathological groups, whereby normal EEG has shown a negative predictive value of 0.825 for AD diagnosis (Class II).¹²⁴ Visual EEG and quantitative EEG (qEEG) can be used in the differential diagnosis between AD and subcortical VaD.¹²⁵ EEG can be required under some circumstances, such as in cases of diagnostic doubt,¹²⁶ but does not constitute a routine exam in dementia.¹²⁷

Recommendations – The EEG can be a useful complement in the diagnostic process (*Practice Option*). It can be used in the differential diagnosis of transient epileptic amnesia vs. transient ischemic attack (*Level B*).

Genetic exam – Vascular ictus of any etiology, whether familial or genetic, is a basic cause of VaD (and of vascular CIND).¹²⁸⁻¹³⁰ A positive family history seems to constitute a risk factor for ictus and genetic influence can vary according to ictus subtype.^{131,132} There is a strong relationship between familiar conditions associated to ischemic and hemorrhagic stroke, as well as those related to connective tissue disease and hematologic diseases, among others.¹²⁸⁻¹³⁰ Single gene causes of stroke are considered relatively rare with multiple genetic influences on VRFs more common, influencing pathogenesis and severity.¹²⁹ The monogenic disorders associated to CVD include CADASIL (*NOTCH 3*), hereditary variant of cerebral amyloid angiopathy (CAA), the frequent sickle cell disease (*HBB**S [homo and heterozygotes] and haplotypes β^S), Fabry's disease (*GLA*), homocystinuria (CBS and other genes), besides other rare conditions.^{26,64,133-136}

Recommendations – The genetic exam for detection of known pathogenic mutations can be carried out when available, mainly for genetic counselling and clinical research purposes. The exams should be done in a specialized center, with appropriate counselling of patient and family members (*Good Practice Point*).

Certain investigations can yield important information for diagnosis (such as concentrations of enzymes, aminoacids, antibodies among others). The biopsy of tissues such as the skin test in the CADASIL, as well as the brain, can be important in primary vasculitis.^{137,138}

Recommendations – Specific exams and tissue biopsy can offer a specific diagnosis in some rarer conditions. The exam should be carried in specialized centers in carefully selected cases (*Good Practice Point*).

Conclusion

The assessment procedures for diagnosing VaD require multi-disciplinary interaction toward reaching a diagnosis. This part of the proposal addressed the analysis of diagnostic criteria, anamnesis, as well as clinical and supplementary exams (neuroimaging and laboratory) used for diagnosing VaD, classified according to proven evidence at various levels.

It should be highlighted that only around half of the population of patients with VCI/VaD present with dementia and the group envisages that the present study can be further refined to enable more precise diagnosis of this condition and that part of the spectrum of CIND and vascular MCI can be extended with the defining of suitable criteria and diagnostic process.

Acknowledgements – We would like to extend our thanks to Dr. Gilberto Sousa Alves and to Dr. Felipe Kenji Sudo, members of the team of the CDA-IPUB-UFRJ for critical review of this paper and to Luzinete Alvarenga, librarian, for organizing the references.

References

- Gauthier S, Rockwood K. Does vascular MCI progress at a different rate than does amnesic MCI? *Int Psychogeriatr* 2003;15(Suppl 1):257-259.
- Hachinski V. Vascular dementia: a radical redefinition. *Dementia* 1994;5:130-132.
- Ingles JL, Wentzel C, Fisk JD, Rockwood K. Neuropsychological predictors of incident dementia in patients with vascular cognitive impairment, without dementia. *Stroke* 2002;33:1999-2002.
- Loeb C. Clinical criteria for the diagnosis of vascular dementia. *Eur Neurol* 1988;28:87-92.
- Meyer JS, Xu G, Thornby J, Chowdhury MH, Quach M. Is mild cognitive impairment prodromal for vascular dementia like Alzheimer's disease? *Stroke* 2002;33:1981-1985.
- Engelhardt E. Demência mista: do conceito ao tratamento. *Rev Bras Neurol* 2004;40:33-54.
- Jellinger KA, Attems J. Is there pure vascular dementia in old age? *J Neurol Sci.* 2010;299:150-154.
- McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. *Alzheimers Dement* 2011 [Epub ahead of print]
- Zekry D, Hawu JJ, Gold G. Mixed dementia: epidemiology, diagnosis, and treatment. *J Am Geriatr Soc* 2002;50:1431-1438.
- Sachdev P. Vascular cognitive disorder. *Int J Geriatr Psychiatry* 1999;14:402-403.
- Rockwood K, Davis H, MacKnight C, et al. The consortium to investigate vascular impairment of cognition: methods and first findings. *Can J Neurol Sci* 2003;30:237-243.
- Engelhardt E, Laks J, Cavalcanti JLS, Moreira DM, Madalen C. Demência vascular. *Rev Bras Neurol* 2004;40:5-25.
- Engelhardt E. Demência vascular. In: Bottino CMC, Laks J, Blay SL (Eds). *Demência e transtornos cognitivos no idoso*. Rio de Janeiro: Guanabara Koogan, 2006: 177-195.
- Erkinjuntti T, Roman G, Gauthier S, Feldman H, Rockwood K. Emerging therapies for vascular dementia and vascular cognitive impairment. *Stroke* 2004;35:1010-1017.
- Jellinger KA. The enigma of vascular cognitive disorder and vascular dementia. *Acta Neuropathol* 2007;113:349-388.
- Zekry D, Duyckaerts C, Belmin J, et al. The vascular lesions in vascular and mixed dementia: the weight of functional neuroanatomy. *Neurobiol Aging* 2003;24:213-219.
- Desmond DW. The neuropsychology of vascular cognitive impairment: Is there a specific cognitive deficit? *J Neurol Sci* 2004;226:3-7.
- Merino JG, Hachinski V. Demência e ictus: loa importância de la enfermedad cerebral coexistente. *Rev Neurol* 2003;36:61-63.
- Tomlinson BE, Blessed G, Roth M. Observations on the brains of demented old people. *J Neurol Sci* 1970;11:205-242.
- Brun A. Pathology and pathophysiology of cerebrovascular dementia: pure subgroups of obstructive and hypoperfusive etiology. *Dementia* 1994;5:145-147.
- Engelhardt E. Demência mista: do conceito ao tratamento. *Rev Bras Neurol* 2004;40:33-54.
- Engelhardt E, Tocquer C, André C, Moreira DM, Okamoto IH, Cavalcanti JLS. Demência vascular. Critérios diagnósticos e exames complementares. *Dement Neuropsychol* 2011;5(Suppl 1):49-77.
- Gorelick PB, Scuteri A, Black SE, et al. American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42:2672-2713.
- Hachinski V, Iadecola C, Petersen RC, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. *Stroke* 2006;37:2220-2241.
- Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: Diagnosis of dementia (an evidence-based review). *Neurology* 2001;56:1143-1151.
- Nitrini R, Caramelli P, Bottino CMC, Damasceno BP, Brucki SMD, Anghinah R. Diagnóstico de doença de Alzheimer no Brasil. Critérios diagnósticos e exames complementares recomendações do Departamento Científico de Neurologia Cognitiva e do Envelhecimento da Academia Brasileira de Neurologia Arq Neuropsiquiatr 2005;63:713-719.
- Nitrini R, Caramelli P, Bottino CMC, Damasceno BP, Brucki SMD, Anghinah R. Diagnóstico de doença de Alzheimer no Brasil. Avaliação cognitiva e funcional. Recomendações do Departamento Científico de Neurologia Cognitiva e do Envelhecimento da Academia Brasileira de Neurologia. Arq Neuropsiquiatr 2005;63:720-727.
- Rockwood K, Parhad I, Hachinski V, et al. Diagnosis of vascular dementia: Consortium of Canadian Centres for Clinical Cognitive Research consensus statement. *Can J Neurol Sci* 1994;21:358-364.
- Madureira S, Verdelho A, Ferro J, et al. Development of a neuropsychological battery for the Leukoaraiosis and Disability in the Elderly Study (LADIS): experience and baseline data. *Neuroepidemiology* 2006;27:101-116.
- Waldemar G, Dubois B, Emre M, et al. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. *Eur J Neurol* 2007;14:1-26.

30. Zhao Q, Zhou Y, Wang Y, Dong K, Wang Y. A new diagnostic algorithm for vascular cognitive impairment: the proposed criteria and evaluation of its reliability and validity. *Chin Med J* 2010;123:311-319.
31. Brainin M, Barnes M, Baron JC, et al. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. *Eur J Neurol* 2004;11:577-581.
32. Organização Mundial de Saúde (OMS) (Classificação Estatística Internacional de Doenças e Problemas Relacionados com a Saúde – Critérios Diagnósticos para Pesquisa) (CID-10-CDP). 10ª edição. 1993
33. American Psychiatric Association Committee on nomenclature and statistics. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, 4th ed. Washington, DC; 1994.
34. Chui HC, Victoroff JI, Margolin D, et al. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. *Neurology* 1992;42:473-480.
35. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Work Group. *Neurology* 1993;43:250-260.
36. Erkinjuntti T, Inzitari D, Pantoni L, et al. Research criteria for subcortical vascular dementia in clinical trials. *J Neural Transm Suppl* 2000;59:23-30.
37. Hachinski VC, Iliff LD, Zilhka E, et al. Cerebral blood flow in dementia. *Arch Neurol* 1975;32:632-637.
38. Chui HC, Mack W, Jackson JE, et al. Clinical criteria for the diagnosis of vascular dementia: a multicenter study of comparability and interrater reliability. *Arch Neurol* 2000;57:191-196.
39. Pohjasvaara T, Mäntylä R, Ylikoski R, Kaste M, Erkinjuntti T. Comparison of different clinical criteria (DSM-III, ADDTC, ICD-10, NINDS-AIREN, DSM-IV) for the diagnosis of vascular dementia. *National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences. Stroke* 2000;31:2952-2957.
40. Wetterling T, Kanitz RD, Borgis K-J. Comparison of different diagnostic criteria for vascular dementia (ADDTC, DSM-IV, ICD-10, NINDS-AIREN). *Stroke* 1996;27:30-36.
41. Wiederkehr S, Simard M, Fortin C, van Reekum R. Comparability of the clinical diagnostic criteria for vascular dementia: a critical review. Part I. *J Neuropsychiatry Clin Neurosci* 2008;20:150-161.
42. Wiederkehr S, Simard M, Fortin C, van Reekum R. Validity of the clinical diagnostic criteria for vascular dementia: a critical review. Part II. *J Neuropsychiatry Clin Neurosci* 2008;20:162-177.
43. Gold G, Bouras C, Canuto A, et al. Clinicopathological validation study of four sets of clinical criteria for vascular dementia. *Am J Psychiatry* 2002;159:82-87.
44. Erkinjuntti T, Inzitari D, Pantoni L, et al. Research criteria for subcortical vascular dementia in clinical trials. *J Neural Transm Suppl* 2000;59:23-30.
45. Erkinjuntti T. Subcortical vascular dementia. *Cerebrovasc Dis* 2002;13(Suppl 2):58-60.
46. Román GC, Royall DR. Executive control function: a rational basis for the diagnosis of vascular dementia. *Alzheimer Dis Assoc Disord* 1999;13(Suppl 3):S69-S80.
47. Holmes C, Cairns N, Lantos P, Mann A. Validity of current clinical criteria for Alzheimer's disease, vascular dementia and dementia with Lewy bodies. *Br J Psychiatry* 1999;174:45-50.
48. Moroney JT, Bagiella E, Desmond DW, et al. Meta-analysis of the Hachinski Ischemic Score in pathologically verified dementias. *Neurology* 1997;49:1096-1105.
49. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging and the Alzheimer's Association workgroup on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:263-269.
50. Smid J, Nitrini R, Bahia VS, Caramelli P. Caracterização clínica da demência vascular. Avaliação retrospectiva de uma amostra de pacientes ambulatoriais. *Arq Neuropsiquiatr* 2001;59:390-393.
51. Fu C, Chute DJ, Farag ES, Garakian J, Cummings JL, Vinters HV. Comorbidity in dementia: an autopsy study. *Arch Pathol Lab Med* 2004;128:32-38.
52. Staekenborg SS, van der Flier WM, van Straaten ECW, Lane R, Barkhof F, Scheltens P. Neurological signs in relation to type of cerebrovascular disease in vascular dementia. *Stroke* 2008;39:317-322.
53. van der Flier WM, Scheltens P. Use of Laboratory and Imaging Investigations in Dementia. *J Neurol Neurosurg Psychiatry* 2005;76(Suppl V):v45-v52.
54. Jagust WJ. Neuroimaging in dementia. *Neurol Clin* 2000;18:885-901.
55. Tartaglia MC, Rosen H, Miller L. Neuroimaging in Dementia. *Neurotherapeutics* 2011;8:82-92.
56. O'Brien JT. Role of imaging techniques in the diagnosis of dementia *Br J Radiol* 2007;80:S71-S77.
57. Scheltens P, Fox N, Barkhof F, De Carli C. Structural magnetic resonance imaging in the practical assessment of dementia: beyond exclusion. *Lancet Neurol* 2002;1:13-21.
58. van Straaten EC, Scheltens P, Barkhof F. MRI and CT in the diagnosis of vascular dementia. *J Neurol Sci* 2004;226:9-12.
59. Ballard CG, Burton EJ, Barber R, et al. NINDS AIREN neuroimaging criteria do not distinguish stroke patients with and without dementia. *Neurology* 2004;63:983-988.
60. Erkinjuntti T, Haltia M, Palo J, Sulkava R, Paetau A. Accuracy of the clinical diagnosis of vascular dementia: a prospective clinical and post-mortem neuropathological study. *J Neurol Neurosurg Psychiatry* 1988;51:1037-1044.
61. Yue NC, Arnold AM, Longstreth WT Jr, et al. Sulcal, ventricular, and white matter changes at MR imaging in the aging brain: Data from the Cardiovascular Health Study. *Radiology* 1997;202:33-39.
62. Cavalieri M, Schmidt R. New development in diagnosis of vascular cognitive impairment. *J Neurol Sci* 2010;299:11-14.

63. Biffi A, Greenberg SM. Cerebral amyloid angiopathy: a systematic review. *J Clin Neurol*. 2011;7:1-9.
64. Longstreth WT Jr, Dulberg C, Manolio TA, et al. Incidence, manifestations, and predictors of brain infarcts defined by serial cranial magnetic resonance imaging in the elderly: the cardiovascular health study. *Stroke* 2002;33:2376-2382.
65. Inzitari D, Pracucci G, Poggesi A, et al. Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort. *BMJ* 2009;339:b2477.
66. Jellinger KA, Attems J. Prevalence and impact of cerebrovascular pathology in Alzheimer's disease and parkinsonism. *Acta Neurol Scand* 2006;114:38-46.
67. Scheltens P, Erkinjuntti T, Leys D, et al. White matter changes on CT and MRI: an overview of visual rating scales. European task force on age-related white matter changes. *Eur Neurol* 1998;39:80-89.
68. Tiehuis AM, Vincken KL, Mali WP, et al. Automated and visual scoring methods of cerebral white matter hyperintensities: relation with age and cognitive function. *Cerebrovasc Dis* 2008;25:59-66.
69. Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for ge-related white matter changes applicable to MRI and CT. *Stroke* 2001;32:1318-1322.
70. Keyserling H, Mukundan Jr S. The role of conventional MR and CT in the work-up of dementia patients. *Neuroimag Clin N Am* 2005;15:789-802.
71. van Straaten EC, Scheltens P, Knol DL, et al. Operational definitions for the NINDS-AIREN criteria for vascular dementia: an interobserver study. *Stroke* 2003;34:1907-1912.
72. de Leon MJ, George AE, Stylopoulos LA, Smith G, Miller D. In vivo studies of hippocampal atrophy in Alzheimer's disease. *J Neural Transmiss (P-D Sect)* 1989;1:34.
73. de Leon MJ, Convit A, George AE, et al. In vivo structural studies of the hippocampus in normal aging and in incipient Alzheimer's disease. *Ann N Y Acad Sci* 1996;777:1-13.
74. Ridha BH, Barnes J, van de Pol LA, et al. Application of automated medial temporal lobe atrophy scale to Alzheimer disease. *Arch Neurol* 2007;64:849-854.
75. Scheltens P, Leys D, Barkhof F, et al. Atrophy of medial temporal lobes on MRI in probable Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J Neurol Neurosurg Psychiatry* 1992;55:967-972.
76. Hsu Y-Y, Schuff N, Du A-T, et al. Comparison of automated and manual MRI volumetry of hippocampus in normal aging and dementia. *J Magnet Res Imag* 2002;16:305-310.
77. Wahlund LO, Julin P, Johansson SE, Scheltens P. Visual rating and volumetry of the medial temporal lobe on magnetic resonance imaging in dementia: a comparative study. *J Neurol Neurosurg Psychiatry* 2000;69:630-635.
78. de Leon MJ, Golomb J, George AE, et al. The radiologic prediction of Alzheimer disease: the atrophic hippocampal formation. *AJNR* 1993;14:897-906.
79. de Leon MJ, George AE, Golomb J, et al. Frequency of hippocampal formation atrophy in normal aging and Alzheimer's disease. *Neurobiol Aging* 1997;18:1-11.
80. Li Y, Li J, Segal S, et al. Hippocampal cerebrospinal fluid spaces on MR imaging: Relationship to aging and Alzheimer disease. *Am J Neuroradiol* 2006;27:912-918.
81. Jack Jr CR, Dickson DW, Parisi JE, et al. Antemortem MRI findings correlate with hippocampal neuropathology in typical aging and dementia. *Neurology* 2002;58:750-757.
82. Bastos-Leite AJ, Scheltens P, Barkhof F. Pathological aging of the brain: an overview. *Top Magn Reson Imaging* 2004;15:369-389.
83. Cho H, Kwon J-H, Seo H-J. Medial temporal lobe atrophy in vascular dementia: Visual temporal lobe rating scale. *Arch Geront Geriatr* 2009;48:415-418.
84. Du AT, Schuff N, Laakso MP, et al. Effects of subcortical ischemic vascular dementia and AD on entorhinal cortex and hippocampus. *Neurology* 2002;58:1635-1641.
85. Fein G, Di Sclafani V, Tanabe J, et al. Hippocampal and cortical atrophy predict dementia in subcortical ischemic vascular disease. *Neurology* 2000;55:1626-1635.
86. Knopman DS, Parisi JE, Boeve BF, et al. Vascular Dementia in a Population-Based Autopsy Study. *Arch Neurol* 2003;60:569-575.
87. Kril JJ, Patel S, Harding AJ, Halliday GM. Patients with vascular dementia due to microvascular pathology have significant hippocampal neuronal loss. *J Neurol Neurosurg Psychiatry* 2002;72:747-751.
88. Zarow C, Vinters HV, Ellis WG, et al. Correlates of hippocampal neuron number in Alzheimer's disease and ischemic vascular dementia. *Ann Neurol* 2005;57:896-903.
89. Engelhardt E, Moreira DM, Laks J. The brain subcortical white matter and aging. A quantitative fractional anisotropy analysis. *Dement Neuropsychol* 2007;3:228-233.
90. Engelhardt E, Moreira DM. A substância branca cerebral. Localização dos principais feixes com anisotropia fracionada direcional. *Rev Bras Neurol* 2008a;44:19-34.
91. Engelhardt E, Moreira DM. A substância branca cerebral. Dissecção virtual dos principais feixes: tratografia. *Rev Bras Neurol* 2008;44:19-34.
92. Engelhardt E, Moreira DM, Alves GS, et al. Binswanger's disease and quantitative fractional anisotropy. *Arq Neuropsiquiatr* 2009;67:179-184.
93. Engelhardt E, Moreira DM, Laks J. The brain subcortical white matter and aging
94. A quantitative fractional anisotropy analysis. *Dement Neuropsychol* 2009;3:228-233.
95. Jellison BJ, Field AS, Medow J, Lazar M, Salamat MS, Alexander AL. Diffusion tensor imaging of cerebral white matter: a pictorial review of physics, fiber tract anatomy, and tumor imaging patterns. *Am J Neuroradiol* 2004;25:356-369.
96. Engelhardt E, Moreira DM, Alves GS, Engelhardt E, Moreira DM. A substância branca cerebral: disseccao virtual dos principais feixes: tratografia. *Rev Bras Neurol* 2008;44:19-34.
97. Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ ACCF/ AHA/ AANN/ AANS/ ACR/ ASNR/ CNS/ SAIP/ SCAI/ SIR/

- SNIS/ SVM/ SVS. Guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary. *Stroke* 2011a;42:e420-e463.
98. Enterline DS, Kapoor G. A practical approach to CT angiography of the neck and brain. *Tech Vasc Interv Radiol* 2006;9:192-204.
 99. Simon A, Megnien JL, Chironi G. The value of carotid intima-media thickness for predicting cardiovascular risk. *Arterioscler Thromb Vasc Biol* 2010;30:182-185.
 100. Gauvrit J, Trystram D, Oppenheim C, Leclerc X. Nouvelles techniques en imagerie vasculaire cervico-encéphalique et médullaire. *J Radiol* 2007;88:472-482.
 101. van Laar PJ, van der Grond J, Mali WP, Hendrikse J. Magnetic resonance evaluation of the cerebral circulation in obstructive arterial disease. *Cerebrovasc Dis* 2006;21:297-306
 102. Vicenzini E, Ricciardi MC, Sirimarco G, Di Piero V, Lenzi GL. Extracranial and intracranial sonographic findings in vertebral artery diseases. *J Ultrasound Med* 2010;29:1811-1823.
 103. Kantarci K, Jack CR Jr, Xu YC, et al. Regional metabolic patterns in mild cognitive impairment and Alzheimer's disease, a ¹H MRS study. *Neurology* 2000;55:210-217.
 104. Engelhardt E, Moreira DM, Laks L, Marinho VM, Rozenthal M, Oliveira Jr AC. Doença de Alzheimer e espectroscopia por ressonância magnética do hipocampo. *Arq Neuropsiquiatr* 2001;59:865-870.
 105. Engelhardt E, Moreira DM, Laks J, Cavalcanti JL. Alzheimer's disease and proton magnetic resonance spectroscopy of limbic regions: a suggestion of a clinical-spectroscopic staging. *Arq Neuropsiquiatr* 2005;63:195-200.
 106. Kantarci K, Petersen RC, Boeve BF, et al. ¹H MR spectroscopy in common dementias. *Neurology* 2004;63:1393-1398.
 107. Martínez-Bisba MC, Arana E, Martí-Bonmatí L, Mollá E, Celda B. Cognitive impairment: classification by ¹H magnetic resonance spectroscopy. *Eur J Neurol* 2004;11:187-193.
 108. Capizzano AA, Schuff N, Amend DL, et al. Subcortical ischemic vascular dementia: assessment with quantitative MR imaging and ¹H MR spectroscopy. *Am J Neuroradiol* 2000;21:621-630.
 109. Dougal NJ, Bruggink S, Ebmeier KP. Systematic review of the diagnostic accuracy of ^{99m}Tc-HMPAO-SPECT in dementia. *Am J Geriatr Psychiatry* 2004;12:554-570.
 110. Talbot PR, Lloyd JJ, Snowden JS, Neary D, Testa HJ. A clinical role for ^{99m}Tc-HMPAO SPECT in the investigation of dementia? *J Neurol Neurosurg Psychiatry* 1998;64:306-313.
 111. Nagata K, Maruya H, Yuya H, et al. Can PET data differentiate Alzheimer's disease from vascular dementia? *Ann NY Acad Sci* 2000;903:252-261.
 112. Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ ACCF/ AHA/ AANN/ AANS/ ACR/ ASNR/ CNS/ SAIP/ SCAI/SIR/ SNIS/ SVM/ SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease. *Stroke*. 2011b;42:e464-e540.
 113. Howard VJ, McClure LA, Meschia JF, Pulley LV, Orr SC, Friday GH. High Prevalence of stroke symptoms among persons without a diagnosis of stroke or transient ischemic attack in a general population the reasons for geographic and racial differences in stroke (REGARDS) study. *Arch Intern Med* 2006;166:1952-1958.
 114. Wadley VG, McClure LA, Howard VJ, et al. Cognitive status, stroke symptom reports, and modifiable risk factors among individuals with no diagnosis of stroke or transient ischemic attack in the reasons for geographic and racial differences in stroke (REGARDS) study. *Stroke* 2007;8:1143-1147.
 115. O'Donnell MJ, Xavier D, Liu L, et al.; on behalf of the INTERSTROKE investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010;376:112-123.
 116. Wiederkehr S, Laurin D, Simard M, Verreault R, Lindsay J. Vascular risk factors and cognitive functions in fondemented elderly individuals. *J Geriatr Psychiatry Neurol* 2009;22:196-206.
 117. Desmond DW, Thomas K, Tatemichi TK, Paik M, Stern Y. Risk factors for cerebrovascular disease as correlates of cognitive function in a stroke-free cohort. *Arch Neurol* 1993;50:162-166.
 118. Raz N, Gunning-Dixon FM, Head D, Dupuis JH, Aker JD. Neuroanatomical correlates of cognitive aging: evidence from structural magnetic imaging. *Neuropsychology* 1998;12:95-114.
 119. Elias MF, Sullivan LM, D'Agostino RB, et al. Framingham stroke risk profile and lowered cognitive performance. *Stroke* 2004;35:404-409.
 120. Andreasen N, Minthon L, Davidsson P, et al. Evaluation of CSF-tau and CSF-Aβ42 as diagnostic markers for Alzheimer disease in clinical practice. *Arch Neurol* 2001;58:373-379.
 121. Parnetti L, Lanari A, Saggese E, Spaccatini C, Gallai V. Cerebrospinal fluid biochemical markers in early detection and in differential diagnosis of dementia disorders in routine clinical practice. *Neurol Sci* 2003;24:199-200.
 122. Stefani A, Bernardini S, Panella M, et al. AD with subcortical white matter lesions and vascular dementia: CSF markers for differential diagnosis. *J Neurol Sci* 2005;237:83-88.
 123. Nägga K, Gottfries J, Blennow K, Marcusson J. Cerebrospinal fluid phospho-tau, total tau and beta-amyloid(1-42) in the differentiation between Alzheimer's disease and vascular dementia. *Dementia Geriatr Cog Disord* 2002;14:183-190.
 124. Robinson DJ, Merskey H, Blume WT, Fry R, Williamson PC, Hachinski VC. Electro-encephalography as an aid in the exclusion of Alzheimer's disease. *Arch Neurol* 1994;51:280-284.
 125. Gawel M, Zalewska E, Szmídt-Sałkowska E, Kowalski J. The value of quantitative EEG in differential diagnosis of Alzheimer's disease and subcortical vascular dementia. *J Neurol Sci* 2009;283:127-133.
 126. Smith SJM. *J Neurol Neurosurg Psychiatry* 2005;76 Suppl II:ii8-ii12.
 127. Fairbairn A, Gould N, Kendall T, et al. Dementia- supporting people with dementia and their carers in health and social care (NICE Guideline 42). London: National Institute for Health and Clinical Excellence, and Social Care Institute for

- Excellence; 2006 (amended 2011). [periodic na internet]. 2011 [acesso em 2011 abr]; 11:52. Disponível em: <http://www.nice.org.uk/nicemedia/pdf/CG42Dementiafinal.pdf>
128. Meschia JF, Brott TG, Brown Jr RD. Genetics of cerebrovascular disorders. *Mayo Clin Proc* 2005;80:122-132.
 129. Razvi SSM, Boné I. Single gene disorders causing ischaemic stroke. *J Neurol* 2006;253:685-700.
 130. Warlow C, van Gijn J, Dennis M, et al. (Eds). *Stroke: practical management*. 3rd ed. Oxford: Blackwell Publishing, 2008.
 131. Jerrard-Dunne P, Cloud G, Hassan A, Markus HS. Evaluating the genetic component of ischemic stroke subtypes: a family history study. *Stroke* 2003;34:1364-1369.
 132. Polychronopoulos P, Gioldasis G, Ellul J, et al. Family history of stroke in stroke types and subtypes. *J Neurol Sci* 2002;195:117-122.
 133. Ashley-Koch A, Yang Q, Olney RS. Sickle hemoglobin (Hb S) allele and sickle cell disease: a HuGE review. *Am J Epidemiol* 2000;151:839-845.
 134. Naoum PS. Sickle cell disease: from the beginning until it was recognized as a public health disease. *Rev Bras Hematol Hemoter* 2011;33:7-9.
 135. Joutel A, Monet M, Domenga V, Riant F, Tournier-Lasserre E. Pathogenic mutations associated with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy differently affect Jagged1 binding and Notch3 activity via the RBP/JK signaling Pathway. *Am J Hum Genet* 2004;74:338-347.
 136. Ballabio E, Bersano A, Bresolin N, Candelise L. Monogenic vessel diseases related to ischemic stroke: a clinical approach. *J Cerebr Blood Flow Metabol* 2007;27:1649-1662.
 137. Joutel A, Favrole P, Labauge P, et al. Skin biopsy immunostaining with a Notch3 monoclonal antibody for CADASIL diagnosis. *Lancet* 2001;358:2049-2051.
 138. Schultz A, Santoianni R, Hewan-Lowe K. Vasculopathic changes of CADASIL can be focal in skin biopsies. *Ultrastruct Pathol* 1999;23:241-247.

GROUP RECOMMENDATIONS IN ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA OF THE BRAZILIAN ACADEMY OF NEUROLOGY

Amauri B. da Silva [UNINEURO, Recife (PE)]; **Ana Cláudia Ferraz** [Serviço de Neurologia do Hospital Santa Marcelina (SP)]; **Analuza Camozzato de Pádua** [Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA); Hospital de Clínicas de Porto Alegre (UFRGS) (RS)]; **Antonio Lúcio Teixeira** [Departamento de Clínica Médica, Faculdade de Medicina da Universidade Federal de Minas Gerais, Belo Horizonte (MG)]; **Ayrton Roberto Massaro** [Instituto de Reabilitação Lucy Montoro (SP)]; **Benito Pereira Damasceno** [Departamento de Neurologia da Universidade Estadual de Campinas (SP)]; **Carlos Alberto Buchpiguel** [Departamento de Radiologia, Faculdade de Medicina da Universidade de São Paulo (SP)]; **Cássio Machado C. Bottino** [Programa Terceira Idade, Instituto de Psiquiatria do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (FMUSP) (SP)]; **Cláudia C. Godinho** [Serviço de Neurologia do Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul (RS)]; **Cláudia Sellitto Porto** [Grupo de Neurologia Cognitiva e do Comportamento da Faculdade de Medicina da USP (SP)]; **Delson José da Silva** [Núcleo de Neurociências do Hospital das Clínicas da Universidade Federal de Goiás (UFG); Instituto Integrado de Neurociências (IINEURO), Goiânia (GO)]; **Elza Dias-Tosta** [Presidente da Academia Brasileira de Neurologia, Hospital de Base do Distrito Federal (DF)]; **Emílio Herrera Junior** [Departamento de Medicina Interna, Faculdade de Medicina de Catanduva (SP)]; **Francisco de Assis Carvalho do Vale** [Universidade Federal de São Carlos (UFSCar), Departamento de Medicina (DMed) (SP)]; **Gabriel R. de Freitas** [Instituto D'or de Pesquisa e Ensino; Universidade Federal Fluminense (RJ)]; **Hae Won Lee** [Instituto de Radiologia, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo e Hospital Sírio-Libanês (SP)]; **Jerusa Smid** [Grupo de Neurologia Cognitiva e do Comportamento do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (FMUSP) (SP)]; **João Carlos Barbosa Machado** [Aurus IEPE - Instituto de Ensino e Pesquisa do Envelhecimento de Belo Horizonte; Faculdade de Ciências Médicas de Minas Gerais (FCMMG), Serviço de Medicina Geriátrica do Hospital Mater Dei (MG)]; **José Antonio Livramento** [Laboratório de Investigação Médica (LIM) 15, Faculdade de Medicina da Universidade de São Paulo (SP)]; **Letícia Lessa Mansur** [Grupo de Neurologia Cognitiva e do Comportamento do Departamento de Neurologia da FMUSP; Departamento de Fisioterapia, Fonoaudiologia e Terapia Ocupacional da Faculdade de Medicina da USP (SP)]; **Márcia Lorena Fagundes Chaves** [Serviço de Neurologia do Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul (RS)]; **Márcia Radanovic** [Laboratório de Neurociências - LIM27, Departamento e Instituto de Psiquiatria da Faculdade de Medicina da Universidade de São Paulo (FMUSP) (SP)]; **Márcio Luiz Figueredo Balthazar** [Universidade Estadual de Campinas (UNICAMP), Faculdade de Ciências

Médicas (FCM), Departamento de Neurologia (SP)]; **Maria Teresa Carthery-Goulart** [Grupo de Neurologia Cognitiva e do Comportamento do Departamento de Neurologia da Faculdade de Medicina da USP; Centro de Matemática, Computação e Cognição, Universidade Federal do ABC (SP)]; **Mônica S. Yassuda** [Grupo de Neurologia Cognitiva e do Comportamento do Departamento de Neurologia da Faculdade de Medicina da USP; Departamento de Gerontologia, Escola de Artes, Ciências e Humanidades da USP (EACH/USP Leste) (SP)]; **Nasser Allam** [Universidade de Brasília (UnB), Laboratório de Neurociências e Comportamento, Brasília (DF)]; **Norberto Anizio Ferreira Frota** [Universidade de Fortaleza (UNIFOR), Serviço de Neurologia do Hospital Geral de Fortaleza (HGF) (CE)]; **Orestes Forlenza** [Laboratório de Neurociências - LIM27, Departamento e Instituto de Psiquiatria da Faculdade de Medicina da Universidade de São Paulo (FMUSP) (SP)]; **Paulo Caramelli** [Departamento de Clínica Médica, Faculdade de Medicina da Universidade Federal de Minas Gerais, Belo Horizonte (MG)]; **Paulo Henrique Ferreira Bertolucci** [Universidade Federal de São Paulo (UNIFESP), Setor de Neurologia do Comportamento - Escola Paulista de Medicina, São Paulo (SP)]; **Regina Miksian Magaldi** [Serviço de Geriatria do Hospital das Clínicas da FMUSP, Centro de Referência em Distúrbios Cognitivos (CEREDIC) da FMUSP (SP)]; **Renata Areza-Fegyveres** [Grupo de Neurologia Cognitiva e do Comportamento do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (FMUSP) (SP)]; **Renato Anghinah** [Grupo de Neurologia Cognitiva e do Comportamento do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (FMUSP); Centro de Referência em Distúrbios Cognitivos (CEREDIC) da FMUSP (SP)]; **Ricardo Nitri** [Grupo de Neurologia Cognitiva e do Comportamento do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (FMUSP); Centro de Referência em Distúrbios Cognitivos (CEREDIC) da FMUSP (SP)]; **Rodrigo Rizek Schultz** [Setor de Neurologia do Comportamento do Departamento de Neurologia e Neurocirurgia da Universidade Federal de São Paulo, Núcleo de Envelhecimento Cerebral (NUDEC) - Instituto da Memória (UNIFESP) (SP)]; **Rogério Beato** [Grupo de Pesquisa em Neurologia Cognitiva e do Comportamento, Departamento de Medicina Interna, Faculdade de Medicina, UFMG (MG)]; **Sonia Maria Dozzi Brucki** [Grupo de Neurologia Cognitiva e do Comportamento da Faculdade de Medicina da Universidade de São Paulo; Centro de Referência em Distúrbios Cognitivos (CEREDIC) da FMUSP; Hospital Santa Marcelina (SP)]; **Tânia Novaretti** [Faculdade de Filosofia e Ciências, Campus de Marília, da Universidade Estadual Paulista (UNESP) (SP)]; **Valéria Santoro Bahia** [Grupo de Neurologia Cognitiva e do Comportamento do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (FMUSP) (SP)]; **Ylmar Corrêa Neto** [Universidade Federal de Santa Catarina (UFSC), Departamento de Clínica Médica, Florianópolis (SC)].