Latin American Delphi Consensus on Vascular Cognitive Impairment: Definitions, Clinical Features, Pathophysiology, Prevention and Treatment

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Abstract

Cerebral vascular disease (CVD) represents the second cause in years of life lost, according to the Global Burden of Disease Study 2015 study. The global report on Alzheimer's disease 2015 estimates that in Latin America there are 9.2 million cases of dementia, with a prevalence of 8.2%. Undoubtedly, Alzheimer's disease is the most frequent cause, followed by vascular dementia (VD) with 15% of the cases, although global data are unknown in Latin America.

Objective: To analyze and present the current evidence on the classification, pathophysiology, diagnosis and treatment of vascular cognitive impairment.

Methodology: A group of experts met in Miami, Florida, in April 2016. The group included Neurologists, Geriatricians and Psychiatrists from the following countries: Mexico, Guatemala, El Salvador, Costa Rica, Peru, Spain, Bolivia, Chile, Paraguay, Colombia, Panama, Venezuela, Italy, the United States, Dominican Republic, Honduras and Nicaragua. The Delphi method was used to review available information (provided months before the meeting), in relation to assigned topics: definition of Cognitive Vascular Impairment (CVI), risk factors, pathophysiology, diagnosis (neuropsychological and imaging) and treatment. For the allocation of evidence and recommendation of available treatments, the GRADE system was used.

The working groups analyzed and discussed available evidence on CVI concerning proposed definitions, risk factors and diagnostic elements. Subsequently, the conclusions of each of the working groups were drafted, which were reviewed by each of the authors and by the rest of the study groups until a global consensus was reached. Once this process was completed, the process of external validation and preparation of the final document was carried out.

The results of this consensus allow the incorporation of the opinion and experience of physicians of different specialties in Latin America regarding the vascular cognitive impairment.

Keywords: Depression; Chronic inflammation; Chronic renal failure; Systemic arterial hypertension; Diabetes mellitus

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Introduction

According to the Global Burden of Disease Study 2015 [1], cerebrovascular disease (CVD) represents the second cause of years of life lost and one of the major causes of disability. This disability includes not only physical limitations and functional

impairment, but also cognitive issues having substantial impact on the patient's quality of life. Latin America is not excluded from the worldwide population aging process; this explains the increase in cardiovascular risk factors and, consequently, higher probability of occurrence of CVD.

There has been major progress in the understanding of cognitive impairment related to vascular pathology. These advances have made it possible to better define vascular cognitive impairment (VCI), and to improve our knowledge of the pathophysiology according to the type of vessel affected (large or small). Also, the wider use of cognitive screening tests for the detection of VCI, even in the early stages, has made it possible to establish the diagnosis in preclinical stages, with the purpose of controlling risk factors.

The Worldwide Report on Alzheimer's Disease 2015 estimates that there are 9.2 million cases of dementia in Latin America, with a prevalence of 8.2% [2]. Certainly, the most frequent cause of dementia is Alzheimer's disease (AD), followed by vascular dementia (VD) with 15% of dementia cases [3]. There are no data by country in Latin America.

The main objective of this consensus was to analyze and summarize current evidence on definition, classification, pathophysiology, diagnosis and treatment of vascular cognitive impairment from a Latin America perspective by a group of Hispanic specialists.

Epidemiology

Stroke is a leading cause of cognitive impairment, disability and mortality in Latin America, although information regarding stroke and vascular dementia in the region is limited [4-7]. Incidence rates of stroke reported in Latin American studies (all adjusted for Segi's world population) range from 76.5 to 110 first-ever strokes per 100 000 per year [8-11]. Stroke prevalence per 1000 population, based on door-to-door surveys, ranges from 1.7 in rural areas to 8.7 among predominantly urban population. In older patients, (aged ≥60), prevalence of stroke ranges from 18.2 to 46.7 per 1000 [12-14]. Considering the high incidence and prevalence of stroke in Latin America, cerebral vascular injury should be expected to be a common cause of dementia and of milder forms of cognitive dysfunction. The prevalence of dementia in Latin America is comparable to that reported in North America. A review of 8 studies on dementia from 6 Latin American countries (Uruguay, Chile, Brazil, Venezuela, Cuba, Peru) reported an overall prevalence of 7.1% (with AD as the most frequent cause), without describing vascular etiology [15]. A report on the global epidemiology of dementia in developed and underdeveloped countries, reported a prevalence of 1.9% (1.0-3.0) in Cuba, 0.9% (0.06-1.78) and 2.2% (1.6-2.7) in Brazil [16]. In Mexico, a study of 110 patients with first-ever stroke, reported a prevalence of vascular dementia (three months after the CVA) of 12%, with a higher prevalence in illiterate patients and lower education [17].

Given the fast and increasing knowledge in this field, it is important to obtain accurate up-to-date data. For this reason,

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a group of experts in cerebrovascular pathology, including neurologists, geriatricians and psychiatrists from several Latin American countries, analyzed the information available in this region, as well as worldwide data regarding cognitive impairment of vascular etiology. The goal of the study group was to establish definitions, diagnosis, classification and recommendations for the prevention and treatment of vascular cognitive impairment (VCI).

Methodology for Study Group's Recommendations

A meeting was held on April 2016 in Miami, Florida, USA,

including a group of Hispanic specialists (vascular neurologists, geriatrics and psychiatrists) of the following countries: Mexico, Guatemala, El Salvador, Costa Rica, Peru, Bolivia, Chile, Paraguay, Colombia, Panama, Venezuela, Dominican Republic, Honduras and Nicaragua. Likewise, Hispanic experts in vascular dementia (Spain, Italy and United States) also participated in the consensus.

The Delphi [18] method was used by the experts, who reviewed the information available (provided months before the meeting) related to assigned topics: definition of VCI, risk factors, pathophysiology, neuropsychological and imaging diagnosis, and treatment. The Grade [19] System was used for assigning the evidence and recommendation of available treatments. The discussion panels analyzed and discussed the available evidence on VCI for proposed definitions, risk factors and diagnostic items. Subsequently, the conclusions of each panel were written, and study groups reviewed them until a global consensus was reached. Once this process was completed, the preparation of the final document was carried out.

Definition from mild vascular cognitive impairment to vascular dementia

In 1988, Reisberg et al. [20] introduced the Global Deterioration Scale (GDS) in which stage GDS 3 indicated the mild progression of cognitive impairment. It was not until 1999, however, when Petersen et al. [21] consolidated the concept of mild cognitive impairment (MCI). MCI emerges then as a prodromal stage of AD, characterized as an interim cognitive stage between normal cognition and dementia. Since then, it is established that to cross the borderline between MCI and dementia, the grade of cognitive dysfunction should be one that impacts on functionality. Therefore, investigations were conducted in this regard, other causes of MCI additionally to AD were recognized, a sub-classification depending on the combination of involved cognitive domains was created, and an attempt was made to associate it with a specific cause (including the vascular cause) as the following step in the diagnostic process [22].

The expansion of spectrum of cognitive impairment with a cerebrovascular origin arises in this way, not only in terms of etiology but also for the severity. Several terms are used to refer to prodromal stages of vascular dementia: mild vascular cognitive impairment (M-VCI), preclinical vascular cognitive impairment, vascular pre-dementia, and non-dementia vascular cognitive impairment [23], referring basically to the same condition but with small differences in the operational definition of the term conferring a great heterogeneity about information of this entity. In 2009, the first special symposium was held at the fourth edition of the Congress of International Society for Vascular Behavioral and Cognitive Disorders (VASCOG), in which the term vascular cognitive impairment (VCI) is proposed to name any cognitive dysfunction with a vascular cause, regardless of its specific etiology and grade of severity, sub-dividing this term into Major Vascular Cognitive Impairment (equivalent to vascular dementia) and Mild Vascular Cognitive Impairment (similar to VCI). In this way, the spectrum becomes more complete in all its dimensions and the prodromal stage of dementia with a vascular

cause is better delimited under the name Mild Vascular Cognitive Impairment [23]. On the other hand, the American Psychiatric Association, in DSM-5, calls it minor neurocognitive disorder [24]. The criterion differentiating a minor from a major disorder is that cognitive difficulties should not influence a person's capability to perform activities of daily life (ADL). It is considered a major neurocognitive disorder when it affects ADL.

The term "cognitive impairment" is classically used for this entity, while the term "neurocognitive" used in DSM-5 emphasizes a condition characterized by cognitive failures not caused by a psychiatric disorder, such as major depression or schizophrenia, but resulting from an "organic" etiology [24]. Thus, VCI is beginning to be recognized as encompassing many diseases, each with different severity and impairment patterns. The recognition that a decline in prior cognitive ability has occurred, as documented by longitudinal data or inferred from a premorbid reference, is implicit in the term.

VASCOG recognizes that there are two requirements for diagnosis of a cognitive disorder: a subjective report and objective evidences of alterations. A clinical visit for a cognitive disorder as the reason for consultation usually results from a concern by the patient and/or an informant who has observed a decrease in the cognitive function. In vascular dementia or major VCI, the subjective report will typically be that the individual depends on other to plan or make decisions, has had to leave complex projects, repeats the same conversation, needs reminders to perform a task, has significant difficulties with expressive or receptive language, has problems to navigate a familiar environment, or has clear alteration in body schema, capability to calculate, read or write [23].

Recommendations

The concept of VCI is a construct covering the entire spectrum of cognitive disorders ranging from mild cognitive impairment (MCI) through fully developed dementia, due to all forms of vascular brain injury. It includes vascular disease as a single etiology, but also in combination with other causes of cognitive impairment, mainly neurodegenerative disorders. Two requirements for diagnosis of a cognitive disorder include a subjective report and objective evidence of cognitive impairment. The criterion to distinguish a minor from a major disorder is that cognitive difficulties do not influence the subject's capability to perform ADLs, whereas these are involved in a major neurocognitive disorder.

Diagnostic Criteria for Vascular Cognitive Impairment

The most commonly used criteria for the diagnosis of vascular dementia are those stated by the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) [25], those adopted by the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) [26], and those contained in DSM-5 and CIE-10. In the last meeting of the VASCOG

in 2013, it was recognized that cognitive disorders of vascular etiology are a heterogeneous set of alterations with different etiologies and clinical manifestations, all of which are considered under the term "vascular cognitive disorders" [23]. There are two critical areas for the diagnosis of vascular dementia: one, the certainty of the presence of a cognitive disorder, and two, the determination that vascular disease is the dominant, if not the only pathology, which accounts for the cognitive disorder.

Clinical characteristics of cognitive syndrome

To clinically establish a predominantly vascular etiology for a cognitive disorder, VASCOG recommends that the following characteristics should be considered in addition to the subjective report and objective evidences of cognitive alterations. The alteration of executive functions, unlike memory disturbances, is often the most outstanding feature of vascular dementia. Memory impairment may not be present in some cases; in others, the disorder in episodic memory is typical (although not exclusive) of vascular dementia. The heterogeneity of pathology in VCI suggests that cognitive deficits will vary according to involved brain area and the way in which lesions appear. This pattern is time-related to strokes, hemorrhages or other vasculopathies [23,24]. However, sometimes it is difficult to establish this temporal relation clinically. For example, cognitive impairment is at its highest level shortly after a brain hemorrhage and it may show a significant improvement over the next three months; but persistence beyond this period is considered necessary for the diagnosis of cognitive impairment. VCI with a gradual onset and slow progression is usually due to small-vessel disease leading to lesions in the white matter, basal ganglia, and/or thalamus [25]. This gradual progression is often marked by acute events that leave subtle neurological deficits such as focal weakness, unilateral incoordination, asymmetrical reflexes, instability, short-step gait, or signs of Parkinsonism [26]. Cognitive changes may be attributed to interruption of cortico-subcortical circuits, and it is likely that speed of information processing, complex attention and executive functions may be involved. White matter ischemic lesions are commonly associated with frontal executive deficits, regardless of their distribution in the brain [27]. Vascular lesions may disrupt thalamus-cortical, striatal-cortical and basal ganglia-prefrontal cortex pathways, as well as cortical and limbic structures; therefore, VCI is often associated with behavioral and emotional disturbances. As these neuropsychiatric features are not specific to vascular etiology, they are not considered as core characteristics in the diagnosis [28]. A clinical history and an appropriate neurological examination may provide additional information, or may be the only objective source of evidence, in the absence of neuroimaging. Thus, a well-documented history of acute stroke is solid evidence of cerebrovascular disease, either from large-vessel disease, or from embolism. Additionally, evidence is also provided by neurological examination showing typical stroke signs, including hemiparesis, facial asymmetry, sensory disorder including visual field defects and pseudobulbar syndrome (supranuclear weakness in facial muscles, tongue and pharynx, spastic dysarthria, difficult swallowing and loss of emotional control) [23]. The following criteria support the presence of CVD, but are not enough by themselves to establish vascular disease as a probable cause of VCI:

1. Early presence of a gait disorder.

2. Urinary urgency or incontinence and other urinary symptoms not explained by urological or non-cognitive neurological disease.

3. Changes in personality and mood, abulia, depression, emotional incontinence, or other subcortical deficits, including psychomotor retardation and abnormal executive function [23,25,26].

Determination of significant cerebrovascular disease (CVD)

This part of the diagnostic process is based on clinical history and neuroimaging. The demonstration of vascular lesions in neuroimaging is essential for higher diagnostic certainty. Absence of neuroimaging data may lead to inaccurate diagnosis. Neuroimaging is also important to rule out less common causes, such as a brain tumor or the normal pressure hydrocephalus (NPH) syndrome [29]. In addition, imaging is important in determining the vascular contribution to AD or to frontotemporal degeneration, as a mixed etiology of cognitive impairment [30]. In general, the evidence of significant vascular pathology is based on computed tomography (CT) or magnetic resonance imaging (MRI), the latter being the most sensitive for this purpose. Neuroimaging findings should be interpreted in the clinical context and their nature, severity and location must be determined. Attempts have been made to define the number of vascular lesions required to support a vascular etiology of cognitive impairment (see section 9.3.1 below, Neuroimaging-supported criteria) [31,32].

Two levels of certainty are recommended for a clinical VCI diagnosis: "probable" and "possible". For a "probable" VCI diagnosis, both clinical and neuroimaging criteria should be met. Although rare, evidence of a genetic cerebrovascular disorder will support a "probable" level of certainty [33,34]. Examples include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL); hereditary endotheliopathy with retinopathy, nephropathy and stroke (HERNS); pontine autosomal dominant microangiopathy and leukoencephalopathy (PADMAL); retinal vasculopathy with cerebral leukodystrophy (RVCL), and type IV A1 collagen disorder (e.g., mutations of *COL4A1* gene) as well as familial forms of cerebral amyloid angiopathy (CAA) [35]. If clinical criteria are met but neuroimaging is not available, the certainty level of the VCI diagnosis remains "possible." By obtaining cerebral imaging, the diagnosis progresses to a greater certainty level ("probable" VCI). The definitive level of diagnosis certainty is obtained through postmortem neuropathological examination. However, the term "definitive" VCI is not proposed in VASCOG recommendations as these recommendations are intended to establish clinical criteria [23].

Differential diagnosis

Given that incidental strokes and vascular leukoencephalopathy are common in the brain of elderly people, it is important to consider other possible etiologies when the patient's cognitive impairment is assessed. When a non-vascular etiology of the dementia is provided by clinical history, physical examination, and/or laboratory investigations then VCI should not be the primary diagnosis but a contributing factor. Often, VCI is an important contributor to several neurodegenerative etiologies of dementia.

A history of early-onset memory deficits and progressive worsening of memory or language (transcortical sensory aphasia), motor skills (apraxia) and perception (agnosia), in the absence of corresponding focal lesions in brain imaging, are more suggestive of AD as the primary diagnosis. Likewise, VCI should not be diagnosed in the presence of other diseases that may induce cognitive impairment, such as a cerebral neoplasia, multiple sclerosis, encephalitis, toxic or metabolic causes. If the patient has major depression that is temporarily related to the onset of cognitive impairment, VCI should not be diagnosed [23]. **Figure 1** depicts the diagnostic algorithm for vascular cognitive impairment proposed by VASCOG.

Recommendations

Diagnosis of mild VCI or vascular dementia should be considered in patients with cognitive impairment and evidence of cerebrovascular lesions. Executive function abnormalities, rather than memory loss, are often the most outstanding feature of VCI. Memory impairment may not be present in some cases of VCI; in others, executive dysfunction with loss-of-set may cause memory problems resulting in episodic memory loss (typical but not exclusive of VCI). The heterogeneity of pathology in VCI suggests that cognitive deficits will vary according to involved brain area and the progression of lesions. When above cognitive profile is temporarily related to a history of ischemic or hemorrhagic strokes the diagnosis of VCI should be confirmed by neuroimaging studies.

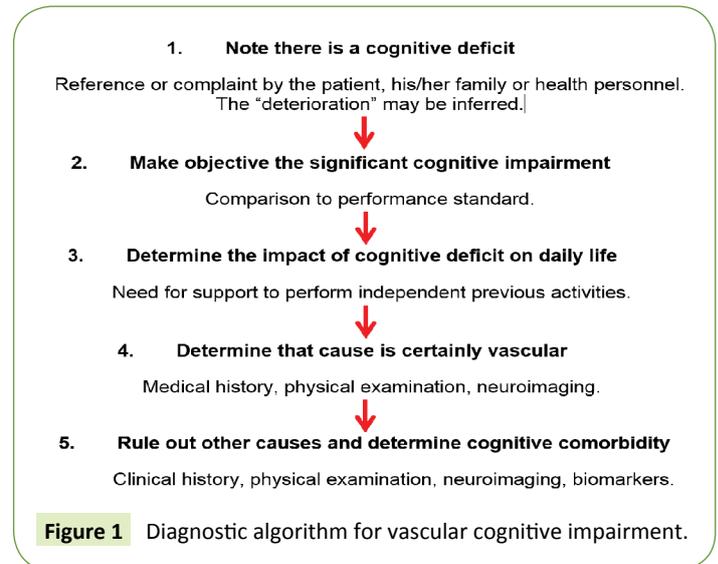# Anatomical Subtypes of Vascular Cognitive Impairment

Anatomically, VCI may be classified as cortical, subcortical or cortico-subcortical considering the site of the predominant location of vascular damage. VCI may also be sub-categorized as ischemic or hemorrhagic, according to the main etiological type of CVD.

Cortical

It is uncommon to find pure cortical VCI, because vascular lesions involving exclusively cortical areas are rare; therefore, they are usually included in the cortico-subcortical group.

Subcortical

Vascular lesions may affect exclusively subcortical regions causing VCI. Several attempts have been made to characterize

1. **Note there is a cognitive deficit**
Reference or complaint by the patient, his/her family or health personnel. The "deterioration" may be inferred.

2. **Make objective the significant cognitive impairment**
Comparison to performance standard.

3. **Determine the impact of cognitive deficit on daily life**
Need for support to perform independent previous activities.

4. **Determine that cause is certainly vascular**
Medical history, physical examination, neuroimaging.

5. **Rule out other causes and determine cognitive comorbidity**
Clinical history, physical examination, neuroimaging, biomarkers.

Figure 1 Diagnostic algorithm for vascular cognitive impairment.

subcortical VCI. The pathological basis of subcortical VCI includes:

1. Multiple lacunar infarctions [26].

2. White matter lesions of vascular origin (Binswanger's disease type) [27].

3. Thalamic dementia due to infarcts located in the thalamus [28].

Cortico-subcortical

Most cases of VCI consist of a combination of cortical and subcortical lesions [29]. In addition, VCI is subdivided into ischemic or hemorrhagic VCI, according to the major etiological type of CVD.

Etiology of Vascular Cognitive Impairment

The increasing recognition of cognitive impairment as a relevant consequence of CVD (beyond classically recognized alterations in motor, sensitive, and other functions) has led to a change in the approach and definition of CVD. Now, there is an appeal to understand the concept of cerebrovascular disease as a construct that may be associated or not with a phenotype of clinical expression for different diseases, according to location of damage, repair capability, previous substrate (prior cognitive threshold, interconnection networks, neuroplasticity), as well as inflammatory and regenerative processes characteristic of the host. Currently, it is considered that there may be "silent" (or rather clinically very subtle) lesions, which beyond the apparent absence of clinical expression, are relevant for cognitive function, and may be an indication of a pathophysiological process that requires treatment.

Parenchymal lesions

Evolution of knowledge on the histo-pathological origin of vascular dementia: Recent progress in histopathology has led

to the emergence of new concepts of cerebrovascular disease relevant to cognition. The dimensions and location of lesions are relevant parameters for VCI expression:

Size of lesion: It is recognized that VCI may occur with a volume of damaged tissue of at least 100 mm^3 regardless the location, or with a lower volume depending on location [30]. Thus, the concept of a strategically-localized infarct arises, in which a lower volume may have a greater cognitive impact due to its location [31,32]. However, the number of infarcts and the volume of damaged tissue correlate with dementia degree (mild = 3 cm^3, moderate = 29 cm^3, severe = 63 cm^3) [33].

Location of lesion: Beyond the volume of damaged tissue, there are cerebral structures that because of their modular function performing a cognitive task or their importance as pathways connecting two cortical areas relevant for cognitive function may cause VCI after relatively small lesions. The following areas are recognized as strategic lesion sites [28,29,34,36,37]:

1. Limbic, paralimbic, frontal and parietal associative heteromodal cortex.

2. Subcortical structures such as basal forebrain, amygdala, (anterior, paramedian) thalamus, basal nuclei.

3. Papez memory circuit.

4. Frontal-subcortical circuits. In particular, prefrontal-caudate nucleus/thalamus/prefrontal circuits.

5. White matter substance (subcortical, deep).

6. Cortico-cortical association fibers.

7. Cortico-subcortical fibers.

8. Commissural fibers (corpus callosum, anterior commissure).

9. Lesions due to disconnection of the previous mentioned structures.

Types of vascular lesion causing cognitive impairment

In the classical concept, major or minor vascular cognitive impairment may be secondary to lesion in small vessels, large vessels or an association of both.

Lesions in large vessels: They are most commonly caused by an atherothrombosis or cardioembolism with occlusion of large cerebral arteries, either extracranial (mainly carotid arteries) or affecting the main intracranial arteries (middle cerebral, anterior cerebral and posterior cerebral arteries). This obstruction causes middle or large-sized strokes causing signs of a neurological disconnection decoupling modules required for the cognitive process. It may also occur due to the presence of multiple infarcts in different locations, which cause a great cortical dysfunction and a loss of different basic functions for cognition (language, memory, executive function, etc.).

Lesions in small vessels: These are classically considered secondary to lipohyalinosis, thickening of arteriolar walls

(arteriolosclerosis), and occlusion of perforating arteries causing a small infarct area (microinfarcts, lacunes), usually in subcortical white matter areas or basal ganglia. It has also been described associated with microatheromatosis in the origin of perforating arteries. Small vessel disease is a major risk factor for developing cognitive impairment and dementia. The following types of small cerebral vessel lesions are recognized:

1. **Lacunar infarct (lacune):** There is no a consensus about the number and location of lacunes required for VCI diagnosis. Possibly, 1 or 2 lacunes do not cause cognitive impairment in older people, and they could be incidental findings. More than two lacunes should be considered necessary to support the VCI diagnosis, except for single lacunes in strategic areas.

2. **Hyperintensity of the white matter:** It is associated with silent neurological and cognitive symptoms.

3. **Perivascular space:** The general enlargement of perivascular spaces is associated with white matter hyperintensity and lacunar infarcts. Some studies have associated the most prominent perivascular spaces with a worse cognitive function.

4. **Microbleeds:** Lobular microbleeds have been included in the research criteria for cerebral amyloid angiopathy. New studies show an association between microbleeds and cognitive impairment.

In the definition of VCI neuropathological substrates, the Newcastle classification considers the following vascular alterations [35]:

1. **Large infarcts or several infarcts:** A result from vascular damage >50 mL of infarcted brain tissue. They include multi-infarct dementia.

2. **Lacunar infarcts or multiple microinfarcts:** Those leaving gliosis and small areas of cavitation. At least 3 infarcts with a minimum size of 0.5 mm are thought to be necessary. This item includes microbleeds, cerebral amyloid angiopathy and diffuse leukoencephalopathy.

3. **Strategic infarcts:** They are present in regions of thalamus and hippocampus, with a lower volume but a high impact on cognitive function.

4. **Cerebral hypoperfusion with hippocampal sclerosis, ischemic anoxic damage, laminar cortical necrosis, or watershed infarcts:** In older subjects, hippocampal sclerosis is accompanied by TDP-43 protein deposits.

5. **Brain hemorrhages:** either intracerebral (mainly lobar) or subarachnoid.

6. **Mixed dementia:** Presence of cerebrovascular changes with AD pathology.

On the other hand, Jellinger summarizes the morphological lesions causing vascular cognitive impairment as describe in **Table 1** [38].

Cerebral microbleeds are easily identified with gradient echo or Swan MRI sequences; these are histopathologically defined as extravasation of blood into the perivascular space. When located in lobar regions, they are related to cerebral amyloid angiopathy, with accumulation of amyloid protein in the wall of arterioles, which become weak and prone to rupture. Occasionally, usually in the context of a genetic alteration, a patient may have hundreds of microbleeds and their presence is a predictor of cognitive impairment [39].

Recommendations

It is critical to establish the size and location of vascular injury in all patients with CVD. It is also necessary to determine the type of vessel affected (large or small), since the damage of the latter includes lacunar infarcts, microbleeds, hyper-intensities or perivascular spaces, which have an impact on the prognosis and treatment of cognitive disorder.

Risk Factors of Vascular Cognitive Impairment

Demographic and genetic factors

The most important demographic predictor for VCI is age; thus, the aging of Latin American populations probably will lead to a higher incidence of VCI. There is no an apparent difference by sex or ethnic factors, and there is a need for reliable geographical studies in Latin America [40-42].

Regarding genetic factors, the role of ApoE epsilon-4 has been studied for its relevance in Alzheimer's disease, but no association with VCI has been established [43,44]. Among genetic diseases, CADASIL stands out, being a non-amyloid small vessels disease associated with cognitive impairment and evidence of alteration in NOTCH gene [45,46].

Lifestyle factors

Diet: It has been proposed that the intake of antioxidants as those contained in vitamin E, vitamin C and beta carotenes in diets including fruits and vegetables, or as supplements, may reduce the risk of VCI [47-49]. However, controlled clinical trials do not show benefit of consuming these antioxidants in the preservation of cognitive function or its impairment reduction [50-52]. The N-3 polyunsaturated fatty acids in fish have antioxidant and anti-inflammatory properties, and they are also the major components of phospholipids of brain cell membranes. Investigations in this respect have shown that the intake of fish for several years (3-6 years) is associated with lesser decline in cognitive function [53-59]. Therefore, a diet rich in polyunsaturated fatty acids in fish oil is recommended. The so-called Mediterranean diet has shown increasing evidence that may reduce cognitive impairment, and it is reasonable to recommend it [60-63].

Table 1 Morphological lesions causing vascular cognitive impairment [11].

Multifocal Disease	Large vessels (large arteries dementia)	**Dementia caused by multiple infarcts:**
		Multiple infarcts
		Watershed infarcts
	Small vessels (small vessels dementia)	**Due to subcortical infarcts:**
		Multiple lacunar infarcts with peripheral lesions in the white matter
		Granular atrophy of cortex (multifocal cortical microinfarcts)
		Lacunar infarcts and multilacunar state
		Binswanger's subcortical leukoencephalopathy
		Subcortical angiopathies (CADASIL and others)
		Due to subcortical plus cortical affection: small multiple infarcts caused by:
		Hypertensive or atherosclerotic angiopathy
		Cerebral amyloid angiopathy with or without hemorrhage
		Collagen or vascular inflammatory disease (systemic or primary vasculitis of nervous system, fibromuscular dysplasia)
		Hereditary forms of cerebral amyloid angiopathy
	Due to hypoperfusion or hypoxia/ischemia	Incomplete white matter infarcts
		Ischemia related to antiphospholipid syndrome
		Hypoxic-ischemic encephalopathy (cortical laminar necrosis, post cardiac arrest, hypotension)
	Associated with venous infarcts	Large hemorrhagic venous infarcts due to venous thrombosis of superior sagittal sinus or great vein of Galen
	Hemorrhagic origin	Subdural hematoma
		Subarachnoid hemorrhage
		Intracerebral hemorrhage
		Multiple microbleeds, especially those subcortical
Focal Disease due to Strategic Lesions	Small infarcts located in functionally important regions such as:	Mesial temporal
		Caudal and thalamic infarcts Fronto-cingular infarcts
		Angular gyrus infarcts
		Strategic areas of white matter

Obesity: Body mass index (BMI) is directly associated with VCI. The *Framingham Offspring Study* showed that the higher the waist-hip ratio was the lower cognitive function during a 12-year follow-up. It is reasonable to recommend the body weight control for preserving cognitive function [64-68]. An increase of BMI is associated with obstructive sleep apnea (OSA), a factor of vascular risk, and a frequent cause of cognitive function impairment. OSA causes subcortical lesions in withe matter by lesions in small brain vessels [69].

Exercise: Regular, long-term physical activity, including vigorous exercise and walking, has been associated with better cognitive function and less impairment with age. Although the *LIFE* study did not yield predicted results for moderate physical activity and cognition improvement in sedentary adults aged 70-89 years, it did show that those at 80 years and older experienced benefits in executive function [70]. Physicians should encourage patients of all ages to optimize their levels of physical activity for the entire life to reduce the risk of developing conditions affecting cognition and other diseases [71]. Therefore, there is a favorable evidence to recommend routine physical activity as a preventive strategy in VCI [72-82].

Smoking: This is a well-known risk factor for ischemic and hemorrhagic cerebrovascular events. Several prospective studies have confirmed higher risk of cognitive impairment in smokers, particularly for some cognitive domains. The evidence indicates that smoking discontinuation is essential for individuals at risk of VCI [83-88].

Alcohol: Some investigations have shown certain benefit in cognition for alcohol users, especially in low to moderate amount, compared to those who do not drink or do it occasionally. For some authors, the benefit would occur primarily in older subjects. However, there is no conclusive data on the amount of alcohol, gender or cognitive domains impacted. Alcohol abuse is associated with all types of CVD. Although moderate alcohol consumption is recommended in patients with VCI [89-95], the experience shows that it is impossible to limit alcohol consumption in patients with cognitive deficit with amnesic predominance; thus, alcohol total abstinence is advisable in these patients.

Depression

Depression may be a comorbidity, a prodromal factor or a consequence of VCI rather that a factor leading to cognitive impairment [96-99]. The Three-City study did not demonstrate an association between VCI and major depression during a four-year follow-up [100]. The *Cardiovascular Health Study* also could not confirm it [101]. Therefore, depression is not currently considered as a risk factor for VCI. Late-life depression (defined as that beginning after age 60) in a cross-sectional study showed that individuals with depression were more likely (20%) to develop vascular dementia [102].

Chronic inflammation

Inflammation is a cardinal process associated with many risk factors of neuronal and vascular damage. Plasma levels of inflammatory proteins, specifically alpha-anti-chymotrypsin and C-reactive protein (CRP), increased prior to the development of vascular dementia after 8 years of follow-up; the CRP levels are high up to 25 years before the onset of vascular dementia. In another study with 4-year follow-up, it was established that a combination of high CRP and interleukin-6 levels resulted in a 3-fold increased risk of developing vascular dementia [103-105].

Chronic renal failure

Several studies with different populations suggest that patients with moderate and severe chronic renal disease have an increased prevalence of cognitive impairment affecting multiple domains. Chronic renal failure is associated with hypertensive encephalopathy and increased risk of CVD. A close relationship between the reduction of glomerular filtration rate and the presence of VCI has been demonstrated. In the Cardiovascular Health Study [106], moderate chronic renal disease was associated with a higher incidence of vascular dementia. However, the association between chronic renal disease and cognitive impairment may be confounded because they share vascular risk factors for small-vessel disease [107-109].

Systemic arterial hypertension

Hypertension is the main risk factor for ischemic and hemorrhagic CVD. The relationship between blood pressure and cardiovascular risk is consistent and independent of other risk factors. More than two thirds of people over 65 are known to be hypertensive. Appropriate control of blood pressure contributes not only to prevent CVD but also to reduce cardiac and renal damage. Antihypertensive treatment has been associated with a reduction in the incidence of CVD from 44% to 35%. Systolic hypertension is recognized as a risk factor to develop VCI and dementia, not only of vascular type but also degenerative dementia such as Alzheimer disease. Hypertension exposes the cerebral microvasculature to pulsatile flow and pressure leading to endothelial damage which causes lipohyalinosis and fibrinoid necrosis. The resulting disruption of perfusion leads to the development of lacunar infarcts or chronic ischemia expressed as a subcortical vascular lesion (leukoaraiosis). There are several cross-sectional and cohort studies demonstrating the close relationship between systolic or diastolic arterial hypertension in the person's half-life and the development of vascular cognitive impairment [110-112].

Studies have shown that there is a "J" or "U" relationship, where the effect of controlling hypertension to prevent the development of VCI is effective when this is done from the middle of the life, but not when it is treated late at an advanced age.

Diabetes mellitus

People with diabetes mellitus (DM) have an increased risk of developing CVD, with a relative risk between 1.8 and 6 depending on the type and severity of DM. Also, patients with DM are about twice as likely to develop dementia. Subjects with DM have lower scores in tests of memory, processing speed and executive functions; these are more apparent with poor glycemic control. MRI studies have shown that patients with DM have more lacunar infarcts and hippocampal atrophy. DM is likely

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to influence cognitive impairment, independently of its role as a vascular risk factor. Hyperglycemia acts through advanced glycation terminal products that have been found in neuritic plaques and neurofibrillary tangles in the early stages of AD. The Rotterdam study indicates that DM doubles the risk of AD and VCI, particularly in subjects with APOE-4 genotype. The presence of repeated and intermittent hypoglycemic episodes in insulin-treated patient causes hippocampal atrophy and cognitive deficit [113-115].

Dyslipidemia

The role of lipid disorders on VCI remains controversial. Dyslipidemias are likely to participate in VCI indirectly through the development of atherosclerosis. Autopsy studies have revealed that patients with AD show atherosclerosis in the circle of Willis in 77% of cases. However, most of the studies assessing the effectiveness of statins in patients with dementia show no improvement [116,117].

Subclinical atherosclerosis

Subclinical atherosclerosis is noninvasively detected, primarily by high-resolution ultrasound measurement of carotid intima-media thickening (IMT). It may also be assessed through studies that measure arterial stiffness (essentially the carotid-femoral pulse wave velocity). IMT has been related with most of the vascular risk factors and the development of vascular events (CVD, coronary). A significant inverse relationship between IMT and cognitive function has been observed; the greater the IMT, the lower the cognitive capacity regardless of age, sex and traditional vascular risk factors. Likewise, studies using carotid pulse wave velocity have found greater arterial stiffness in subjects with cognitive impairment [118,119].

Cardiovascular disease

VCI risk has been associated with atrial fibrillation (AF), heart failure, chronic renal disease and coronary and peripheral arterial disease. AF impacts on the development of VCI not only through the production of cardioembolic ischemic cerebral events, but also with an increased risk of AD and VCI, independently, although the mechanism is unknown. It has been shown that cerebral volume in subjects with AF is lower than in controls without AF. It has been stated that this is a consequence of hypoperfusion when AF has a rapid ventricular response or because of the presence of microembolism. One of the causal factors of AF is unsuspected and untreated OSA. On the other hand, the reduction of cardiac output has been associated with a decrease in cognitive functions, in particular executive functions. It has been proposed that chronic hypoperfusion is the major contributor but more studies should be conducted. Coronary artery disease is also associated with an increased risk of VCI [120,121]. In addition, coronary artery bypass surgery is associated with early cognitive impairment (post-surgery) and increased risk of dementia in the median term. Finally, peripheral arterial disease measured through the ankle-arm index is also associated with a higher risk of vascular dementia [122,123].

Sleep disorders

From Nurses' Health Study [124], it was observed that women who sleep 5 hours or less or those who sleep 9 hours or more at night had a higher risk of MCI compared to women who sleep 7 hours. OSA is one of the risk factors most frequently missed when evaluating patients with VCI [125].

Hyperhomocysteinemia

Several studies have shown that high levels of homocysteine are associated with an increased risk of cardiovascular events, either coronary or cerebrovascular. There is also evidence that hyper- homocysteinemia is related to VCI, either through cerebrovascular damage or directly. Hyperhomocysteinemia may be determined by genetic-environmental factors, mutations in critical metabolism enzymes, mainly metylentetrahydrofolato-reductase (MTHFR) and deficiency or low levels of vitamins involved in metabolism such as vitamin B12 and folic acid. Some families with *MTHFR* gene mutations may have a history of depression, suicide and alcoholism, as well as elevated homocysteine. The treatment of hyperhomocysteinemia with cobalamin (vitamin B12), pyridoxine (vitamin B6) and folic acid (vitamin B9) in patients with minimal cognitive deficit stops the progression to dementia and cerebral atrophy typical of AD [126-128].

Recommendations

VCI has been associated with several preventable vascular risk factors such as hypertension, sedentary lifestyle, obesity, smoking, diabetes mellitus, hypercholesterolemia and obstructive sleep apnea. Management of these risk factors remains a practical approach to reducing VCI.

Diagnostic Methods for Vascular Cognitive Impairment

Diagnostic neuropsychological tests in vascular cognitive impairment

Cognitive impairment is characterized by a wide range of cognitive deficits, but there is a predominance of executive dysfunction [129,130]. Therefore, the neuropsychological protocols should be sensitive to various domains, with an emphasis on executive function assessment. For Latin American population, it is important to consider several aspects to conduct the cognitive assessment: (a) education level; (b) standardized and validated tests for study population; (c) time to conduct it, and (d) personnel who will conduct assessments (doctor, psychologist).

There are no specific and universally accepted tests for VCI diagnosis. There are three recommended protocols lasting 60 minutes, 30 and 10 minutes. The 60-minute test may be used in studies requiring a detailed analysis of capabilities in the cognitive domains. Physicians may use the following tests during visits:

30-minute tests: The clinical screening tools in patients with suspected VCI include the following [131]:

1. Phonological fluency

2. Semantic fluency

3. Montreal Cognitive Assessment (MoCA)

4. Digits in regression

5. Mini-Mental State Examination (MMSE)

6. Trial Making Test A and B (TMT A and B)

7. Hopkins Verbal Learning Test (HVLT-R)

10-minute tests: These are instruments to be used by primary care physicians, nurses, and other healthcare professionals, to allow rapid detection of VCI:

1. **Mini-Mental State Examination (MMSE):** This is a widely used method to estimate the intellectual status but insufficient to assess the executive function; its 3-word memory test is insensitive to early detection of memory impairment in patients with VCI.

2. **MoCA (Montreal Cognitive Assessment):** This short test designed to detect cognitive impairment in older adults has a maximum score of 30 points. The MoCA test is sensitive to subcortical damage. It may also be administered via telephone [132,133]. The MoCA in Spanish (MoCA-S) has been validated in some countries of Latin America. In Mexico, validation showed a sensitivity of 80% and specificity of 75%, with cut-off point of 26 for MCI (area under the curve 0.886 p <.001). For the dementia group, it showed a sensitivity of 98% and specificity of 93%, with cut-off point of 24. (Area under the curve 0.998 p<0.001) [134]. In Colombian elderly subjects with low education, the MoCA-S had a high reliability but scores were strongly dependent on years of education, social and cultural factors [135]. A compensation of 3-4 points was needed for subjects with<6 years of education [136].

Neuropsychological tests proposed for VCI, by cognitive domain

Execution/activation (planning, decision making, working memory, response to feedback or error corrections, inhibition/predominant habits, mental flexibility):

1. **Semantic fluency [137]:** A test related to left posterior parietal-temporal region.

2. **Phonological fluency [138]:** Reflecting integrity of left dorsolateral frontal region.

3. **Wechsler Adult Intelligence Scale (WAIS) – Digits:** It evaluates processing speed and activation.

4. **Trail Making:** It is a test of exploration, visual-motor tracking, divided attention and cognitive flexibility. The test is very sensitive to the presence of cognitive impairment [139].

5. **Hopkins Verbal Learning Test (HVLT-R) [140]:** It may provide strategic learning measures reflecting the dorsolateral frontal function in addition to episodic memory rates.

6. **Frontal Assessment Battery (FAB):** It includes six subtests, which correlate with frontal lobe function. The performance in these six subtests may give a composite global score, which assesses the severity of the dysexecutive syndrome [141].

7. **Clock drawing test [142,143]:** The common errors in executive function showed in this test include incorrect placement of the hands, graphic problems (diffuse lines, small circle, correction attempts) and difficulties in spacing numbers.

Visuospatial (visoconstructive skills, visual perception): This neuropsychological test is performed through Rey-Osterreith complex figure [144]. This task requires organization and visuo-perceptual skill. The primary visuospatial test is administered by copying the Rey-Osterreith figure, and the memory test was selected as a supplementary measure.

Language: Evaluation includes expressive language such as naming objects, finding words, fluency, grammar and syntax, as well as receptive language. Common language tests are the following:

1. **The Boston Naming Test (BNT) [145]:** It diagnoses the presence and type of aphasic deficit, allowing global assessment of difficulties in all the areas of language. Evaluation of naming capability is by visual confrontation.

2. **Semantic fluency:** It may serve as a less structured lexical retrieval task.

Learning and memory: It includes immediate memory, recent memory, free recall, evoked recall and recognition, as well as long-term semantic and autobiographical memory and implicit learning. Tests include:

1. **HVLT-R (Hopkins Verbal Learning Test – Revised):** This is the preferred learning test. Its strengths include a multiple-choice form and a short administration time. The HVLT-R does not include an interference list or a key recall. Clinical studies have shown that it is sensitive to cognitive impairment related to VCI.

2. **Wechsler Memory Scale:** It allows assessment of verbal learning capability, short- and long-term retention and recognition capability, as well as other more specific aspects such as the interference effect or the trend to respond with false positives; it is sensitive to VCI [146,147].

3. *RAVLT* **(Rey Auditory Verbal Learning Test) or Rey test for verbal and auditory learning:** It assesses recognition, interference, learning curve, immediate and delayed memory.

To establish a difference between static cognitive deficits following a cerebrovascular disease and the progressive dementia syndrome, it is advisable to conduct serial neuropsychological tests, usually after a year of evolution.

1. **California Verbal Learning Test-II:** Useful for evaluating episodic verbal learning and memory [148].

Recommendations

There are no specific and universally accepted tests for the diagnosis of VCI. There is no ideal neuropsychological test and the assessment should include sensitive tests for each type of cognitive disorder. MoCA is a sensitive screening test to detect VCI and should be used to detect early forms of this disorder. Other recommended tests include those of semantic and phonological fluency, FAB and clock test. All the tests should be standardized and validated for the study population. The assessment of illiterate or low education patients is a problem that requires the urgent development of appropriate evaluation methods in Latin America.

Neuroimaging studies

The main neuroimaging choices to study VCI are MRI and CT scan. MRI is particularly sensitive in the evaluation of cognitive disorders characterized by small-vessel lesions. The minimum acceptable field strength is 1.0 Tesla, but ≥ 1.5 T is preferred. The following sequences are required: weighted in T1 and T2, FLAIR, and gradient echo. The first 3 sequences provide information on the anatomy, the presence of an infarct and other pathologies, while the gradient echo identifies the presence of bleeding, including small, chronic and/or acute hemorrhages. Neuroimaging findings should be interpreted in a clinical context considering the infarct nature, severity and location. The use of Arterial Spin Labeling (ASL) imaging for cerebral blood flow in non-contrast MRI is a promising technique in VCI.

Neuroimaging-supported criteria to determine vascular dementia: Although it is accepted that VCI may rarely occur without evidence of cerebral infarcts in the neuroimaging studies, these lesions are usually present. A single strategic stroke or an extensive stroke having effects in several cognitive domains may be necessary to cause a VCI. If multiple-stroke disease is a cause of VCI, at least one should occur outside the cerebellum. Ideally, there should be a temporary association between the stroke and the onset of cognitive impairment, in such a way that the ischemic lesion precedes the impairment within previous three months, and that this impairment extends beyond this period.

California criteria [26]: Two or more ischemic infarcts, with at least one of them outside the cerebellum, are required to diagnose vascular dementia.

NINDS-AIREN criteria [25]: Multiple large vessel infarcts or a strategic infarct (occurred at angular gyrus, thalamus, basal forebrain, or in the posterior or anterior carotid region) or lacunar infarcts in the white matter or basal ganglia, or extensive periventricular lesions in the white matter are required.

Newcastle criteria [35]: The presence of >3 lacunar infarcts should be appropriate evidence of causality, especially with co-existing white matter disease.

Characteristics of lacunar infarcts in neuroimaging [149]: Lacunar infarct is better detected with a FLAIR sequence in MRI, which shows the lesion as a small hypointense area surrounded by a hyperintense halo, although the fluid in the central cavity is not suppressed in FLAIR sometimes and may appear completely hyperintense. Lacunar infarct is commonly considered as a 3-15 mm lesion, but definitions vary with maximum diameters of 2 cm. The VCI harmonization group recommends consider "lacunes" up to 1 cm, with the main characteristic of being ischemic lesions or small hemorrhages in the deep white matter of a perforating arteriole. Given their small size, the MRI sequence with adjacent slices ≤ 4 mm is required to detect adequately these lesions. In CT, lacunar infarcts are small hypodense lesions (i.e., well defined), but given the poor CT spatial resolution, these lacunar lesions may remain unnoticed. It is important not confuse lacunar lesions with Virchow-Robin perivascular spaces, although these findings may really represent and early stage of small vessel disease with an underlying microvascular degeneration.

Vascular lesions in sub-cortical white matter: In CT, white matter lesions are hypodensities (leukoaraiosis). In MRI, they are hypointense areas in T1 and hyperintense in T2-weighted images. Subcortical vascular leukoencephalopathy may be focal or multifocal, and as these types of lesions become more extensive, they may converge and involve a large area of white matter. Basal ganglia and thalamus also show these lesions. When vascular leukoencephalopathy is mild, these lesions appear as small "caps" in frontal or occipital horns of lateral ventricles, or as thin "rings" surrounding these structures [150]. However, these images are not specific to vascular leukoencephalopathy, as comparable patterns may be observed in several pathologies, including multiple sclerosis, cerebral edema, neurosarcoidosis, brain lesion caused by radiation, etc. Despite the diverse listing of differential diagnoses, there is clinical evidence and pathological data suggesting that most of these brain lesions in older subjects have an ischemic origin. These lesions are caused by arteriolosclerosis, lipohyalinosis and fibrinoid necrosis of the small vessels, and particularly along the perforating arteries, with or without occlusion. Vascular leukoencephalopathy is highly prevalent in the brains of older people and even middle-aged individuals; thus, only extensive lesions are clinically significant. If vascular leukoencephalopathy is focal and visible only in T2, it is unlikely to be significant enough to explain the development of cognitive disorder. Some researchers have suggested that at least 25% of total white matter should be affected to support a vascular dementia diagnosis. Therefore, it is difficult to have precise rules for relating leukoencephalopathy to mild VCI or vascular dementia. A general rule is that these lesions should be extensive and confluent and the above descriptions are considered as patterns of subcortical vascular involvement. With the development of new MRI techniques such as diffusion tensor imaging, it has been shown that white matter that appears normal in T2 may also have anisotropy or abnormal diffusivity matching with the neuropathology and be relevant to support the presence of cerebrovascular damage in the presence of cognitive alterations [151,152].

Intracranial hemorrhagic lesions: Cognitive disorders have been associated with intracerebral hemorrhage, subarachnoid hemorrhage, and subdural hematoma. VCI has also been associated with cortical and subcortical microbleeds, which may be related to hypertension or cerebral amyloid angiopathy.

This angiopathy is a consequence of the accumulation of Aβ40 (different from A42 that forms the plaques in AD), which is deposited in the intima and the media of the vessel, producing fragility and hemorrhage, but also predisposes to thickening of the artery, which causes ischemia [153]. These lesions are better visualized in MRI Eco-GRE sequence. Microbleeds associated with hypertension are in the deep brain nuclei and brainstem, while those associated with amyloid angiopathy and Alzheimer's disease has usually a lobar location. As microbleeds are not uncommon in cognitively normal older adults, the attribution of VCI to microbleeds should be done only when these lesions are numerous and after careful exclusion of other causes of cognitive impairment.

Cerebrovascular assessment by other studies: Doppler ultrasonography technology provides useful information on the state of cervical and intracranial arteries, complementing the information of parenchymal brain lesion identify by neuroimaging studies. Transcranial Doppler is a dynamic study of cerebral blood flow velocities that helps to determine functional characteristics and to deduce structural aspects as well. Brain perfusion is also assessed through single photon emission computed tomography and CT with xenon contrast. Positron emission tomography (PET) allows imaging through regional glucose metabolic rates, using 18F-fluorodeoxyglucose (FDG-PET). It is useful for establishing the differential diagnosis of some types of cognitive disorders. There is no characteristic pattern in patients with vascular dementia, and its current usefulness is to rule out another type of dementia [154]. More recently, amyloid imaging with compounds such as radiolabeled Pittsburgh Compound B (C-PIB) has gained a great interest and has been proposed as a biomarker for AD imaging. ASL imaging in brain MRI measures cerebral blood flow in a noninvasive way, it does not require any contrast injection, and does not expose the patient to radiation; furthermore, there is a good correlation between ASL and FDG-PET.

Recommendations

It is essential to have a neuroimaging study when assessing the patient with cognitive impairment for probable vascular etiology. Brain CT should be performed in all cases. Cerebral MRI is the ideal study to characterize small-vessel lesions and it should be requested considering the individual clinical context for each patient.

Genetic and inflammatory biomarkers and their neuropathological correlation in vascular cognitive impairment

In patients with VCI, several biomarkers have been investigated for early detection, to discriminate neuropathological findings, to estimate prognosis and to monitor disease progression or therapeutic response [155,156]. In these circumstances, markers related to genetic factors and inflammatory mediators involved in the etiopathogenesis of VCI are of interest.

The analysis of cerebrospinal fluid (CSF) biomarkers, along with clinical and neuroimaging information, may enhance the diagnosis of different brain disorders causing cognitive impairment [156]. Vascular dementia is generally related to the following biomarkers in CSF:

Total tau: It is a dynamic marker of the intensity of axonal degeneration/damage. Its levels increase in Creutzfeld-Jakob disease, and it may also be found in dementia associated with VCI, cerebral trauma and AD [157-159]. The usefulness of tau protein in the diagnosis of vascular dementia is to exclude other etiologies, so that there are no cut-off points for the diagnosis of vascular pathology [160].

Light sub-unit of neurofilament protein: It is the best biomarker in CSF for subcortical axonal damage/degeneration. It occurs at high concentrations in vascular dementia, frontotemporal dementia and different inflammatory disorders (multiple sclerosis, dementia-AIDS complex). The combination with an AD biomarker indicates the presence of mixed dementia [155,161-164].

CSF and serum albumin concentration index: It is the most defined biomarker of integrity of the blood-brain barrier. There is usually an elevation of this ratio in patients with vascular dementia (particularly due to subcortical vessel disease) [156,159,164].

Levels of tumor necrosis factor alpha (TNF-α): This proinflammatory cytokine mediates myelin damage. Its levels increase in patients with subcortical vascular dementia and correlate to sulfatide levels (a white matter degradation marker). It is found potentially high in subcortical vascular dementia [165].

Sulfatides: They identify possible white matter demyelination.

Metaloproteases [166]: They increase when there is vascular or white matter damage. It has been demonstrated that high levels of some of them allow prediction of the evolution of vascular impairment. High levels of metalloproteinase MMP-9 are associated with worse prognosis for VCI compared to those with a stable disease and low MMP-9 levels. According to imaging studies, there is also a positive correlation between MMP-9 mean values and the volume of infarct or ischemia. MMP-9 and MMP-2 levels depend on the occlusion time of vascular bed, which may extend, expand or cause worse vascular damage.

Other cytokines: The assessment of interleukin IL-1 is considered important, along with tumor necrosis factor alpha. It may be associated with worsening of vascular impairment. They could also be correlated to the measurement of IL-10 and IL-1ra (IL-1 receptor antagonist interleukin) by exerting a potential neuroprotective effect. IL-6 is present in acute ischemia and reflects the extent of the infarct; it could also be correlated to severity of vascular damage in the patient with VCI.

Anti-inflammatory prostaglandin 15-Dpgj2: The high levels of this prostaglandin may correlate with better prognosis in the evolution of VCI.

Homocysteine: Its persistent elevation matches with the potential presence of a deleterious inflammatory process that may perpetuate and enhance the vascular damage with the corresponding progression of cognitive impairment [167].

C-reactive protein: It is known to be associated with a poor long-term functional prognosis when it is increased in the acute

phase of the cerebrovascular event. Although this marker cannot predict the stroke progression, it is an excellent, independent predictor of mortality and morbidity in CVD evolving into VCI.

Non-specific biomarkers used for distinctive diagnosis of vascular cognitive impairment: The finding in CSF of low levels of amyloid beta 42 amino acids, with high levels of hyperphosphorylated tau, or biochemical signs of neuro-inflammation (increased white blood cells, production of IgG or IgM) indicates non-vascular dementia and may be useful as negative biomarkers for the diagnosis of pure vascular dementia. However, the implementation of CSF biomarkers in the diagnostic process of vascular dementia requires standard methods in the collection, storage and measurement of the sample [155-157].

Recommendations

At present, there is no biomarker capable of establishing the diagnosis of VCI. The utility of these biomarkers is to confirm the presence of neuronal damage or inflammation. More studies are needed to identify a sensitive and specific marker to establish the early diagnosis of VCI.

Mixed Dementia

The concept of mixed dementia refers to the coexistence of a typical degenerative disease (e.g., Lewy body dementia, frontotemporal dementia, Alzheimer's disease) and vascular dementia. Alzheimer's disease shows the strongest evidence of its interrelation with vascular lesions.

The term mixed dementia represents a challenge for clinicians and even for neuropathologists, and expresses the increasing difficulty to isolate a "pure" type of dementia (vascular versus Alzheimer's), especially in preclinical stages. At the same time, it represents a model for the study of two-way interaction between vascular lesions of different types (atherosclerosis, arteriolosclerosis, amyloid angiopathy) and neuronal degeneration [168]. Vascular lesions can cause both neurodegeneration and its typical markers (e.g., neurofibrillary tangles, β-amyloid), as similarly neurodegenerative pathology can accumulate β-amyloid compromising the cerebral vasculature and cause vascular lesions. As long as the classification of pure neurodegenerative or vascular forms remains as the initial step to classify dementias, we will be forced to define a "hybrid" called "mixed dementia". The proposed approach for the classification is described in **Figure 2** and consists of determining first whether dementia (meeting the accepted criteria) is associated or not with overt cerebrovascular lesions, to rule out pure forms in this way. Subsequently, a distinction is established among those showing evidence of vascular lesion, those having more clinical and paraclinical features of degenerative dementia despite vascular lesions, and those having more clinical and paraclinical characteristics of vascular dementia but also with evidence of neurodegenerative pathology.

Association between cerebrovascular disease and Alzheimer's disease

Epidemiological studies show that Alzheimer's disease and cerebrovascular disease share similar risk factors including hypertension, diabetes, smoking, apolipoprotein E epsilon 4 isoforms, hypercholesterolemia, chronic nephropathy and, mainly, age [169,170]. Cardiac risk factors, in particular atrial fibrillation and congestive heart failure, have also been associated with the pathogenesis and progression of Alzheimer's disease [168-177].
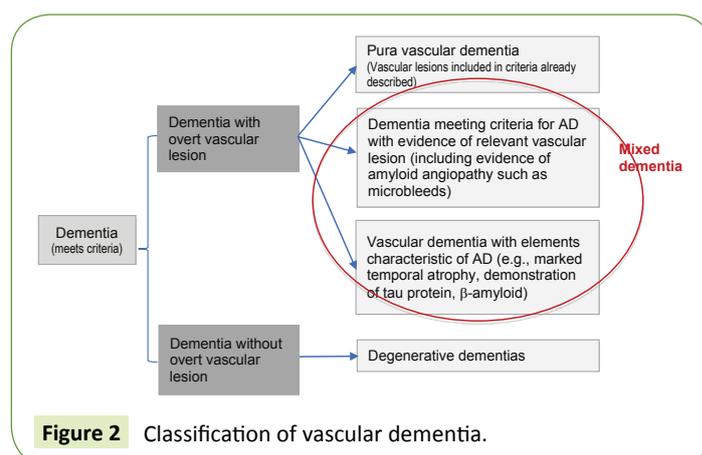
A study in Mexican patients with Alzheimer's disease and mixed dementia demonstrated after multivariate analysis that hypertension (OR: 1.92, p= 0.009), white matter disease (OR: 3.61, p= 0.001) and lacunar infarcts (OR: 3.35, p = 0.014), were associated with mixed dementia [178].

Different studies have documented the overlapping of cerebrovascular disease and Alzheimer's disease, an association even stronger in Braak stages with a lower density of neurofibrillary tangles. The autopsy study with 5,715 cases of the National Alzheimer's Coordinating Center confirmed data on the prevalence of cerebrovascular disease and Alzheimer's disease, and the deleterious additive or interacting effect of vascular pathology and Alzheimer's disease on cognition [179-181].

Likewise, aging itself has a deleterious effect on the cerebral vasculature similar to that caused by Alzheimer's disease, as when drainage of soluble β-amyloid is affected it leads to accumulation in vascular walls and parenchyma, with the already known consequences on homeostasis of neuronal environment and cerebral perfusion [106,182]. In addition, the presence of cerebrovascular disease has been associated with worse cognitive performance in patients with AD, and neuropathological studies have documented that cerebrovascular disease reduces the dementia threshold in subjects with pathological diagnosis of AD [183,184]. Thus, it has been proposed that CVD contributes to neuropathological changes of AD, including selective cerebral atrophy and accumulation of abnormal proteins such as β-amyloid. On the other hand, subcortical AD and CVD may independently affect cortical atrophy [185-187].

Type of vascular lesions more associated with mixed dementia

In brains with AD and mild CVD (primarily degenerative dementia), most of the cerebrovascular lesions are lacunar infarcts in basal

Figure 2 Classification of vascular dementia.

ganglia and white matter, with multiple microinfarcts. This pattern of topographic distribution of cerebrovascular lesions is very similar to that observed in "pure" vascular dementia (vascular dementia without histopathology of AD greater than expected for the age). Sixty-eight percent are lacunar infarcts involving thalamus or hippocampus, and only 32% are extensive cortico-subcortical infarcts.

In contrast, mixed dementia may be accompanied by lobar infarcts and multiple cortico-subcortical lesions (57%) rather than subcortical lacunar infarcts or strategic infarcts (43%). This suggests different pathogenic mechanisms between these two entities, which give greater importance to microangiopathy in pure vascular dementia or AD with mild cerebral vascular disease than in mixed dementia, as described in **Table 2**, which compares common lesions in AD, VD and mixed dementia [188].

The combination of two or more pathological processes may influence the severity of cognitive impairment in such a way that cerebrovascular lesions may unmask dementia at preclinical stage in patients with Alzheimer's disease. However, apparently small cerebrovascular lesions occurring in 10-50% of the adult population without cognitive impairment cannot cause dementia by themselves.

Physiopathogenesis proposed for mixed dementia

Microvascular changes in the brain of older people and AD induce cerebral perfusion alteration, in particular, a decrease in regional blood flow, reduction of glucose transport and utilization, with loss of vascular innervation and a special impact on the deficits in cholinergic neurotransmission in the case of AD. Likewise, there is damage in neurovascular regulation, ultrastructural changes in capillaries and basement membranes due to deposition of β-amyloid, with disruption of the blood-brain barrier and alteration of β-amyloid clearance. The succession of these events and other deleterious effects create a vicious circle, which finally produces structural disintegration through infarcts, lacunar lesions and vascular lesions in white matter, which compromise neuronal metabolism, with mitochondrial energy deficit and oxidative stress, promoting the degradation of proteins, lesions in cytoskeleton with formation of neuritic plaques and deposition of β-amyloid. These factors induce cerebral atrophy and the consequent cognitive impairment.

On the other hand, atherosclerosis and amyloid angiopathy cause changes in the self-regulation of microvasculature, leading to loss of myelin, frequently observed in elderly people's brains, suggesting shared risk factors for all pathological changes observed in AD and cerebrovascular disease. White matter lesions can be caused by both cerebral vascular disease (hypoperfusion) and AD (retrograde degeneration). These lesions progress with age, represent a considerable risk factor for cognitive impairment and lead to impairment in frontal functions regardless of their location [189-191].

The most common clinical expression in neuropsychological tests is combined; i.e., they exhibit characteristics of a subcortical

Table 2 Vascular lesions comparison between AD, VD and mixed dementia.

Pathology	AD (%)	VD (%)	Mixed dementia (%)
Total infarcts	10-20	100	30-40
Small vessel disease	Approx. 50	>50	>50
Lacunar infarcts	30-46	70	60-70
White matter pathology	40	80	70-80
Intracerebral hemorrhage	10-15	15	10
Cerebral amyloid angiopathy	98	30	Approx. 90
Loss of cholinergic markers	75	40	Approx. 70
Atherosclerosis	45-60	60	Approx. 60
AD: Alzheimer's Disease; VD: Vascular Dementia. Adapted from Jellinger KA, Attems J (J Neurol Sci 2007, 257: 80-87).			

cognitive profile, as well as of cortical. However, regardless of the predominance of the clinical pattern showed by the patient, in almost all the cases there is a clear compromise of frontal and prefrontal functions.

Diagnostic criteria for mixed dementia

The clinical criteria for the diagnosis of mixed dementia are diverse and pose difficulties for the study of this condition as an independent entity. The International Classification of Diseases (ICD-10) does not consider mixed dementia an isolated entity but includes it in the AD section "G30.8: Other Alzheimer's-type Diseases (atypical and mixed forms)".

The classification by the *Consortium to Establish a Registry for Alzheimer's Disease* (CERAD) [192] does not consider mixed dementia in its classification, while the criteria of the *Alzheimer's Disease Diagnostic and Treatment Centers* (ADDTC) require the evidence of a CVD closely related to dementia (referred to without a time framework), in addition to the typical pathology of AD [26]. The NINDS-AIREN criteria suggest to demonstrate an evidence of memory compromise and at least two other cognitive areas, in addition to an evidence of cerebrovascular lesion (focal neurological signs and infarcts/lesion in brain white matter imaging), and that the onset of dementia occurs within 3 months from the occurrence of the cerebrovascular event [25].

In 2011, the AHA/ASA recognized that vascular and degenerative pathologies are frequent and coexisting disorders in elderly people, and that separately each adds to the other the possibility of developing cognitive impairment and dementia with overlapping clinical and neuroimaging phenotypes. Additionally, there is a need to resolve the concerns by establishing a relationship between neuroimaging findings and postmortem studies [169]. First, by improving the resolution capacity of neuroimaging studies, as they currently can detect macroscopic infarcts of more than 3 mm, but fail to detect microscopic infarcts and small vessels disease (such as arteriolosclerosis). Second, some vascular pathologies may represent vascular or degenerative process, as degeneration of white matter, measured in FLAIR sequence and by diffusion, as well as microbleeds, measured by echo-gradient sequence, are associated with both cognitive vascular disorder and AD [193-195], and pathology studies have

shown that white matter degeneration and microbleeds are related to lipohyalinosis [196,197].

On the other hand, changes in hippocampal volume may be related to AD-type or vascular pathology [198] in such a way that the atrophy of hippocampus may occur in response to a degenerative or vascular process [199]. The different criteria used so far for mixed dementia around the world are detailed comparatively in **Table 3** [24-26,200-202].

Gold et al. [203] compared the clinical findings to the neuropathological diagnosis in 113 elderly subjects with dementia undergoing autopsy. The subjects were neuropathologically classified with mixed dementia if they met the criteria for AD and for vascular dementia. All the clinical criteria examined had a different behavior when diagnosing mixed dementia behavior. The proportion of cases neuropathologically diagnosed with mixed dementia which have been clinically classified as vascular dementia was 54% for ADDTC, 29% for the NINDS-AIREN criteria, and 18% for the Hachinski scale. The Hachinski scale allowed to exclude more cases of mixed dementia but failed to identify many cases of vascular dementia. The ADDTC and NINDS-AIREN criteria were more sensitive to detect vascular dementia, but less able to distinguish between vascular dementia and mixed dementia. Mixed dementia was better excluded with NINDS-AIREN than with ADDTC. The authors reported that mixed dementia has a significant effect on the acuity of the diverse clinical criteria. Recent data from the same group have confirmed that clinical criteria for vascular dementia are not equivalent to those for mixed fementia and work very differently with respect to mixed dementia detection. Furthermore, restrictive criteria such as ICD-10 or the probable category of ADDTC and NINDS-AIREN do not correlate significantly to histopatological diagnoses. In a meta-analysis, Moroney et al. found that Hachinski scale distinguished well between AD and VD, but it had difficulties with mixed dementia diagnosis [204].

From the above mentioned, we conclude that there are no validated and accepted clinical-pathological criteria for the diagnosis of mixed dementia and therefore there are only recommendations for its diagnosis, many of them based on histopathological findings. Jellinger considers the following suggestions [188]:

1. *National Institute of Aging* (NIA) criteria assessing plaques (including diffuse plaques as neuritic-NPs) in neocortex and hippocampus per unit, corrected for age.

2. Criteria based in the semi-quantitative assessment of plaques and NFTs in neocortex and hippocampus.

3. CERAD criteria using the semi-quantitative NPs count adjusted for age, to which the clinical history of dementia is added to establish the probability of AD.

4. Topographic categorization of neuritic (neurofibrillary) changes, with 6 stages: entorhinal (1 and 2), hippocampal (3 and 4) and neocortical (5 and 6).

5. Quantitative criteria of the University of Washington, a modification of the NIA consensus criteria 1985.

Table 3 Criteria for mixed dementia.

Source	Criteria
Hachinski scale	Scale based on clinical data: ≤ 4 = AD, ≥ 7 = VD; middle score of 5 or 6 = MD
International Classification of Diseases (ICD 10th edition)	Cases metting criteria for AD and VD.
Diagnostic and Statistical Manual of Mental Disorders (DSM-V)	Cases with criteria for Alzheimer-type primary degenerative dementia and clinical or neuroimaging data for VD.
Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC)	Presence of isquemic cerebrovascular disease and a second cerebral or systemic disorder.
National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche´ et l'Enseignement en Neurosciences (NINDS-AIREN)*	Typical AD data associated with clinical and radiological evidence of cerebrovascular disease.
AD: Alzheimer's Disease; VD: Vascular Dementia. MD: Mixed Dementia. *They do not call it MD but AD with cerebrovascular disease.	

6. The guides of NIA and Ronald and Nancy Reagan Research Institute of the Alzheimer's Association (NIA-RI) make a postmortem diagnosis of AD by combining the CERAD and Braak criteria. This leads us to establish a low probability (CERAD = 0-A, Braak = 1-2), medium probability (CERAD B, Braak 3-4) or high probability (CERAD C, Braak 5-6) that dementia is caused by AD.

7. VD/VCI cluster all the cases where cognitive compromise can be attributed to cerebrovascular disease (CVD) and it is greater than that expected for normal aging. VD would be a type located at the end of VCI, where cognitive compromise is severe enough to interfere with social and occupational activities.

VCI is a "continuum" emerging from the initial appearance of vascular risk factors, which generate CVD and then cerebrovascular damage, which according to its location causes different types of cognitive compromise. CVD includes arteriolosclerosis, atherosclerosis, amyloid angiopathy and CADASIL, while cerebrovascular damage relates to a brain lesion caused by CVD, which will depend on the size of the involved artery, i.e., lesion in large arteries and lesions in small arteries. In the first case, it can cause total occlusion and we will have an infarct, with a deficient clinical picture, generally motor, that along the months may evolve into cognitive impairment, which is known as post-VCD dementia (or post-stroke dementia). In the case of cerebrovascular damage caused by lesions of small arteries, we have two probable settings, which finish in the classic lacunar state syndromes and Binswanger syndrome, depending on complete or incomplete artery occlusion. Thus, a pathological examination is important for, first, confirming or detecting cerebral vascular damage, especially for lesions that cannot be detected by neuroimaging techniques (small infarcts, selective neuronal loss, microinfarcts); second, confirming or identifying the type of underlying CVD (arteriolosclerosis, amyloid angiopathy, etc.); and third, to assess the presence or matching extension of an AD-type pathology. Jellinger proposes

a combination of autopsy-proven AD and multiple lacunar infarcts or lesions causing cerebrovascular damage in cortex, basal ganglia, thalamus, hippocampus and white matter, with approximately 30-50 mL of infarcted cerebral volume.

Due to the difficulty to make available technological devices (MRI with more Tesla units, Pittsburgh compound B, etc.) and a histopathology in most of the cases, an *operating definition* for mixed dementia is recommended to use it in a stepped way as follows:

1. Carrier of cardiovascular and cerebrovascular risk factors, either known or not by the patient at the time of initial evaluation.

2. Defined diagnosis of dementia, without considering the neuropsychological phenotype.

3. MR neuroimaging with 1.5 Tesla or greater demonstrating vascular lesions other than:

- Lobar infarct or hemorrhage

- Strategic lesions (e.g.: thalamic)

- Extensive vascular lesions (Fazekas scale 3)

- Age, which has a greater importance in the pathophysiology of both diseases. The detection at early stages, at a younger age, has a greater relevance as after the age of 85 most of the cases are defined and advanced, and even the cases of degenerative dementia will already have a not negligible "lesion burden". On the other hand, hereditary forms of Alzheimer's disease have an early onset. For example, the mean age at onset is 46.8 years (range: 36-42 years) with an average duration of up to 8 years with a fatal outcome in patients with dominant E280A mutation of the presenilin-1 gene present in Antioquia (Colombia). These cases are characterized by the presence of minimal cerebrovascular lesions, in contrast to forms of late-onset AD [205].

Strategies to Prevent Vascular Cognitive Impairment

There are several therapeutic interventions that can prevent, delay the onset or slow down the progression of vascular cognitive impairment, which are described in **Table 4** [206-208]:

The main impact on the modification of natural history of cognitive alterations related to cerebrovascular disorders is achieved when therapeutic interventions are applied in the early stages of cognitive impairment [209], but especially when they are conducted before VCI develops. These measures not only help to prevent VCI but also have favorable results in neurodegenerative disorders such as Alzheimer's disease.

Health care efforts should be focused on primary preventive measures, including the modification of known vascular risk factors [206,207,210,211]. The direct impact on the improvement of cognitive functions through the appropriate control of smoking, hypertension [212,213] and the Mediterranean diet

[60-63] is especially relevant.

Different studies and systematic reviews have demonstrated that cognitive training is an effective way to objectively improve the cognitive function. A Cochrane review in 2012 [214] points out that cognitive stimulation programs demonstrated benefits in the treatment of patients with mild MCI and moderate dementia. A relation between mental activity developed early, in the middle and late life, and a significant reduction of dementia has been observed in the advanced age (OR: 0.54). A multivariate approach to reducing risk for cognitive decline was tested in the FINGER study (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) [215]. Authors found overall that cognitive performance improved significantly with a multi-component lifestyle intervention involving physical activity, nutritional guidance, cognitive training, and social activities, as well as management of vascular risk factors.

Recommendations

In the absence of a disease-modifying treatment or cure for CVI, reducing the risk of developing vascular dementia takes on added importance. There is sufficiently strong evidence to conclude that a healthy diet, management of modifiable vascular risk factors (diabetes, obesity, smoking, and hypertension) and lifelong learning and cognitive training may reduce the risk of cognitive decline and may reduce the risk of dementia.

Pharmacological Treatment

The main randomized controlled trials in patients with VCI treated with pharmacologic interventions show some benefit for improving cognition. However, none have received regulatory approval particularly because the lower effect sizes compared to AD. Considered the previous aspects, the main drugs are briefly reviewed [216].

Table 4 Strategies for therapeutic intervention in vascular cognitive impairment.

Interventions	Evidence quality (GRADE System)	Strategy recommendations
Lifestyle factors		
Smoking discontinuation	B1	Reasonable
Moderate alcohol intake	B1	It can be reasonable
Weight control	B1	It can be reasonable
Physical activity	A1	Advisable
Mediterranean diet	B1	Advisable
Physiological factors		
Treatment of hypertension	A1	Advisable
Treatment of hyperglycemia	B1	It can be reasonable
Treatment of hypercholesterolemia	B1	It can be reasonable
Other interventions		
Vitamin supplements	A2	Not demonstrated
Cognitive stimulation	B1	Advisable
Multimodal intervention	B1	Advisable

Donepezil

It is a specific and reversible acetylcholinesterase (AChE) inhibitor that increases acetylcholine (ACh) levels. Several studies using donepezil for vascular dementia have been published. Two randomized, double blind, controlled studies in 1219 patients with possible or probable vascular cognitive impairment should be mentioned; in them, 5 or 10 mg daily of the drug were administered for 6 months, compared to placebo. Significant benefits were found in cognition, global function and functionality in activities of daily life in patients receiving donepezil, thereby inferring its effectiveness [217,218].

Recommendation Grade: A1

Rivastigmine

This pseudo-irreversible inhibitor of acetylcholinesterase and butyrylcholinesterase, facilitates cholinergic neurotransmission by slowing degradation of acetylcholine released by functionally intact cholinergic neurons.

A double-blind, randomized clinical trial assessed the effectiveness of rivastigmine treatment (3-12 mg/day) compared to placebo in patients with vascular dementia for 6 months. The results did not provide consistent efficacy [219]. The other trial compared rivastigmine (9 mg/day) with placebo in patients with mild cognitive impairment for 6 months of treatment, providing some benefit in the executive functioning [220].

Recommendation Grade: B2

Galantamine

It is a competitive, reversible acetylcholinesterase inhibitor. It shows allosteric modulation of the nicotinic receptor (nAChR), and bonds to nAChR in a place other than acetylcholine (ACh). When it merges simultaneously with ACh at their respective binding sites, the presynaptic nicotinic receptor becomes more sensitive to ACh and amplifies its response.

Galantamine has been assessed in two clinical trials crucial to know the benefits of this drug. A double-blind, randomized clinical trial used galantamine (24 mg/day) in 592 patients with "pure" vascular dementia as "mixed" vascular dementia for 6 months of treatment, showing a benefit over placebo in cognition, global assessment, activities of daily life and behavioral symptoms [221]. The other trial in 788 patients diagnosed with "pure" vascular dementia assessed the effectiveness of galantamine treatment with 24 mg/day, compared to placebo for 26 weeks. The results showed a benefit in cognition and executive functions with galantamine [222,223].

Recommendation Grade: B1

Memantine

It is a non-competitive, voltage-dependent, antagonist with low/moderate affinity for NMDA (N-methyl-D-aspartate) receptors; it blocks the excitotoxic effects of pathologically increased glutamate tonic levels that may cause neuronal dysfunction.

Two clinical trials compared memantine (20 mg/day) to placebo in mild to moderate vascular dementia for 28 weeks. Data analysis showed an improvement in cognitive functions, but not in the global clinical impression nor in the activities of daily life, in those treated with memantine [224,225].

Recommendation Grade: B2

Nimodipine

It binds to L-type calcium receptors and reduces the number of open channels transporting calcium ions through cell membrane. It has a vasodilating action on arterioles and can modulate other calcium dependent processes such as the release of acetylcholine. The binding sites are in neurons and cerebrovascular cells, and their action can influence both neural conduction and brain blood flow.

A Cochrane 2002 review analyzed three studies using nimodipine (90 mg/day) between 12 and 24 weeks in patients with vascular dementia, and a benefit was found in some cognition and global assessment scales [226] A multicenter, double-blind, randomized study comparing nimodipine (90 mg/day) to placebo for the treatment of subcortical vascular dementia for 52 weeks was published, without finding a benefit in the cognition scales [227].

Recommendation Grade: B2

Citicoline

It stimulates the biosynthesis of structural phospholipids in the neuronal membrane. It inhibits the activation of certain phospholipases (A, A2, C and D) and preserves the neuronal energy reserve, inhibiting apoptosis and stimulating the synthesis of acetylcholine. It improves the brain function by interacting with several neurotransmitters and receptors, as well as due to its vasoactive and antibinding properties.

A systematic Cochrane 2005 review included 14 clinical trials; the effects of citicoline on the treatment of cognitive, emotional and behavioral deficits associated with chronic cerebral disorders in older people were analyzed. There were difficulties due to heterogeneity of the articles, but even with these technical difficulties there was evidence of certain benefit for memory, behavior and global clinical impression in the medium and short term, especially in patients with cognitive deficits associated with cerebrovascular disorders [228]. Subsequently, a randomized, open-label study comparing citicoline to placebo for 12 months was published to assess the effectiveness of citicoline in preventing post-stroke cognitive impairment in patients who had a first ischemic stroke event; benefits in executive function and guidance were found [229,230]. Simultaneously, the IDEALE study was published, comparing oral citicoline (1000 mg/day) to placebo for mild VCI for 9 months. The results obtained showed a slight but non-significant difference in the geriatric depression scale score, and also that MMSE score remained unaltered over the time [17,231]. A two-year treatment and follow-up study with citicoline published in 2016 having as objective to measure the quality of life and cognitive status in patients who had suffered a first stroke demonstrated that citicoline (1 g/day) is associated

with an improved quality of life (EuroQol-5D) in both elderly and young patients, and significantly improved the cognitive status (p = 0.005) after two years of treatment, following a first stroke. In addition, only the citicoline treated group (vs. standard measures) sustained cognitive improvement after the first year of treatment [232].

Recommendation Grade: B2

EGB 761 (*Ginkgo biloba*).

Ginkgo biloba has antioxidant, vasoactive and neurotransmitter-modulating properties.

In the Cochrane 2002 review, it was concluded that the benefit of *Ginkgo biloba* (unspecified dose) for people with dementia or cognitive impairment is inconsistent and unreliable. Subsequently, a multicenter, double-blind, randomized study was conducted to demonstrate the effectiveness of *Ginkgo biloba* (240 mg/day) compared to placebo in 410 patients with mild-moderate dementia (vascular dementia or Alzheimer's disease) for 24 weeks. The results showed a benefit of using *Ginkgo biloba* compared to placebo in cognition, psychopathology, functional measures and quality of life for patients and caragivers [233].

Recommendation Grade: B2

Cerebrolysin

It has neurotrophic mechanisms such as antiapoptopic activity, modulation of anti-inflammatory response, reduction of free radicals, modulation of CDK5 and GSK3β activity, neuroplasticity and neurogenesis.

In a randomized, double-blind, prospective clinical trial conducted with cerebrolysin in 242 patients over 50 years of age diagnosed with mild-moderate vascular dementia, 20 mL intravenous cerebrolysin were administered once daily for 24 weeks, comparing to placebo. The cerebrolysin treatment showed that cognitive function, overall function, daily life activities and executive functions improved significantly [234,235]. Subsequently, a Cochrane 2013 review was published and analyzed 6 studies using 10-30 mL intravenous cerebrolysin daily with a variable duration (age range: 60-71 years) in patients diagnosed with mild-moderate vascular dementia, and a benefit in some scales of cognition and global assessment was found [236].

Recommendation Grade: C2

Piracetam

It is a cyclic derivative of gamma-aminobutyric acid (GABA) that can cross the blood-brain barrier and is selectively concentrated in the cerebral cortex. It restores the fluidity in the cell membrane, inducing the lipid reorganization and stimulating the synthesis of membrane phospholipids and choline uptake in the muscarinic cholinergic nerve endings. At low doses, piracetam increases the utilization of oxygen and glucose through the energy pathways of adenosine triphosphate (ATP). At higher doses, it opposes to platelet aggregation and has antithrombotic effects.

The Cochrane 2001 review did not demonstrate any benefit with piracetam in patients with dementia or cognitive impairment [237].

Recommendation Grade: C2

Propentophylline

This acts on the blood-brain barrier by blocking adenosine and inhibiting the phosphodiesterase enzyme; it also inhibits the production of free radicals and reduces the activation of microglial cells.

A Cochrane 2003 meta-analysis concluded that there is no sufficient evidence to demonstrate beneficial effects with this drug on cognition, global function and activities of daily life in people with Alzheimer's disease and/or vascular dementia [238].

Recommendation Grade: C2

Recommendations

Treatments of vascular cognitive impairment have shown modest cognitive improvements with donepezil, galantamine and memantine, although these improvements have uncertain clinical significance.

Conclusion

There is insufficient data to recommend the use of these drugs in a generalized way in patients with vascular cognitive impairment, so their indication must be individualized.

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