Chapter

Vascular Brain Disease in Geriatric Neuropsychiatry

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Abstract

Vascular brain diseases are a significant cause of dementia, and their presence, alone or associated with degenerative conditions, increases the risk of conversion to progressive cognitive decline. Neuropsychiatric manifestations vary according to the affected brain territory and disrupted neuronal circuits. In the current chapter, epidemiological prevalence, the harmonization of the diagnostic criteria of vascular subtypes, and the impact of age and socio-demographic aspects are critically reviewed. Another explored topic refers to the diagnostic and therapeutic approach. Structural imaging, including magnetic resonance (MRI) and computer tomography (CT), and a thorough neuropsychological and clinical exam, may help establish the differential diagnosis and substantially impact clinical evolution. Treatment involves various strategies, including controlling cardiovascular and metabolic risk factors, such as hypertension, atrial fibrillation, cardiopathies, and adopting a healthy lifestyle. Treatment relies on preventive and health promotion strategies related to the timely control of vascular risk factors and symptomatic approaches. The use of acetylcholinesterase inhibitors aims at stabilizing symptoms and is recommended in all stages of dementia.

Keywords: brain, vascular, cognitive impairment, geriatric neuropsychiatry

1. Introduction

The concept of vascular dementia (VaD) is a diagnostic category that emerged in the late 1980s to characterize dementia secondary to cerebrovascular disease [1]. The construct was later expanded into the Vascular Cognitive Involvement complex (VCI), a continuum ranging from Vascular Mild Cognitive Impairment (VMCI) to dementia [2]. This chapter will comprehensively address the main clinical, diagnostic, and therapeutic aspects of VCI.

2. Epidemiology

2.1 Population studies

Recent studies estimated that between 5 and 7% of the world's elderly population suffers from dementia, with a higher frequency in Latin America (8.5%) and a slightly lower prevalence in sub-Saharan Africa (2–4%) [3]. Considering the high social and economic impact of the condition, especially in these regions with fast population aging, knowledge of the epidemiology of dementia has become fundamental for planning health policies [4, 5].

From an etiological point of view, cerebrovascular disease is the second most common cause of acquired cognitive impairment and dementia, occurring both as a single mechanism of brain damage and contributing to cognitive decline in neurodegenerative dementias [6]. Cerebral arteriosclerosis was considered the leading cause of "senile dementia" until the 1960s when Alzheimer's Disease (AD) became recognized as the most prevalent brain pathology affecting those individuals [7, 8]. Recently, cognitive impairment of vascular origin has once again attracted the interest of researchers, driven mainly by the growing concern with metabolic conditions (systemic arterial hypertension, diabetes mellitus, dyslipidemia and obesity) and their effects on target organs [9, 10]. The incidence rate of dementia appears to be declining in western developed countries, which has been hypothesized to result from continued improvements in older adult education and advances in health care, including efficiently controlling metabolic diseases [11, 12].

Challenges for understanding and interpreting the epidemiological aspects of VCI to include the lack of harmonization of the nomenclature and diagnostic criteria used in the studies. **Table 1** lists some of the primary population studies produced between 2000 and 2012, which have estimated the prevalence of VaD in different countries. A meta-analysis reported that VaD occurs in 1.6% of individuals over 65 years of age and constitutes 26% of the total number of people with dementia in western countries [13]. Conflicting results across studies could be identified, mostly derived from different sources of diagnostic criteria employed: when the National Institute of Neurological Disorders and Stroke and *l'Association Internationale pour la Recherche et l'Enseigne* (NINDS-AIREN) criteria was adopted, the prevalence of VaD was 1.6%; conversely, the adoption of Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) criteria yielded a prevalence of 2.6% [4].

2.2 Brain vascular changes and cognition

One study demonstrated that 83.3% of individuals with dementia due to subcortical vascular disease initially presented focal or mild changes in cognition, with low impact on functionality, which would be analogous to the concept of Mild Cognitive Impairment due to AD [14]. Vascular Cognitive Impairment non Dementia, another construct of prodromal VaD, presented a prevalence of 2.6–8.5% in samples older than 65, configuring the most common clinical form among VCI cases [15].

In addition to etiological characteristics, other aspects may impact the prevalence of VaD in studies, such as age and geographic aspects, i.e., the inclusion of populations from long-term care facilities and the presence of comorbid brain conditions with neurodegenerative processes. Some studies demonstrated an increase in VaD prevalence with aging, although lesser than that observed in AD. It was suggested that the prevalence of VaD would double every 5.3 years, while AD would present a prevalence twice as high every 4.3 years [6]. Consistently, prevalence rates below 1% were identified in some studies that included samples younger than 65 years of age, whereas in a study evaluating a 95-year-old group, the prevalence was 15.7% (**Table 1**). However, conflicting results could be found in the literature on the relationship between aging and VaD. A European study, for example, showed that the prevalence of VaD reduced when populations aged 60 and 90 were compared—15 and 8.7%, respectively [16]. In addition, the variation in the prevalence of VaD between the eighth and tenth decades of life was not significant in one study (from 10.2 to 9.9%) [16, 17]. Mixed dementia, on the other hand, showed that prevalence between these age groups increased, advancing from 4.7 to 7.1% of subjects [16, 17]. Another study conducted in the USA showed that VaD was responsible for 21% of dementia cases among those 80 years of age, but this rate corresponded to only 16% of cases older than 80. Studies evaluating the prevalence

Country	Author, year	Sample (n)	Diagnostic criteria	Age (years)	Prevalence
China	Wang W et al., 2000	3728	DSM-III-R, ICD-10	≥65	1.37%
	Zhang ZX et al., 2005	34807	MINDS-AIREN	≥65	1.1%
	Zhao Q et al., 2010	17018	DSM-IV, NINDS-AIREN	≥55	0.79%
	Jia J et al., 2014	10276	DSM-IV, NINDS-AIREN	≥65	0.79%
South Korea	Lee DY et al., 2002	643	DSM-IV	≥65	2%
	Jhoo JH et al., 2008	1118	DSM-IV, NINDS-AIREN	≥65	1%
	Kim KW et al., 2011	8199	DSM-IV, NINDS-AIREN	≥65	2%
Japan	Yamada T et al., 2001.	3715	DSM-III-R, NINDS-AIREN	≥65	1%
	Ikeda M et al., 2001	1162	DSM-IV	≥65	2.4%
	Meguro K et al., 2002	1654	DSM-IV, ADDTC, NINDS-AIREN	≥65	1.6% (NINDS-AIREN) and 2.6% (ADDTC)
	Wada-Isoe K et al., 2009	120	DSM-IV, NINDS-AIREN	≥65	1.7%
Thailand	Wangtongkum S et al., 2008.	1492	DSM-IV, NINDS-AIREN	≥45	0.29%
Sri Lanka	de Silva HA et al., 2003	703	DSM-IV	≥65	0.57%
Turkey	Arslantaş D, Ozbabalik D, 2009	3100	CID-10	≥55	4.29%
Spain	Vilalta-Franch J et al., 2000	1460	CAMDEN	≥70	6.23%
	García García et al., 2001	3214	DSM-III-R, NINDS-AIREN	≥65	1.8%
	Bofill E et al., 2009	877	DSM-IV, NINDS-AIREN	≥80	6%
Denmark	Andersen K et al., 2000	3346	DSM-III-R	65–84	1.3%
Sweden	Börjesson-Hanson A et al., 2004	338	DSM-III-R	95	15.7%
USA	Plassman BL et al., 2007	856	DSM-III-R, DSM-IV	≥71	2.43%
Brazil	Herrera Jr. et al., 2002	1656	NINDS-AIREN.	≥65	0.66%
	Bottino CM et al., 2008	1563	DSM-IV	≥60	2%
Egypt	The Callaway HN et al., 2012	8173	DSM-IV-TR	≥50	0.64%

Table 1.
Population studies of VAD prevalence.

of early-onset dementia (starting before 65 years old) have also documented controversial results. VaD was shown to be the leading cause of early-onset dementia in a Japanese retrospective study, affecting 42.5% of the cases [18], while a Spanish study, which evaluated the incidence of dementia in individuals aged 30–64 years,

reported that VaD was responsible for only 13.8% of cases; therefore, occurring less frequently than AD (42.4%) and dementia secondary to general medical conditions (18.1%) [19].

Geographic issues may affect the prevalence of VaD across studies. Classical studies have recorded the high prevalence of VaD in Japan and China, which would account for 50% of dementia cases, overcoming the frequency of AD [13]. Recent studies, however, have not confirmed such findings. It is currently accepted that, as observed in other countries, AD is the most common etiology of dementia in these regions. Meguro et al. [20] have argued that epidemiological studies previously conducted in Japan had overestimated the occurrence of VaD, probably due to categorizing mixed dementia within the group with cerebrovascular-related cognitive impairments [4]. Consequently, VaD/AD prevalence ratios significantly decreased in individuals 75 years old or more in studies conducted in Japan from 1985 to 2005 (2.1 in 1985; 1.2 in 1992; 0.7 in 1998 and 0.7 in 2005) [21]. In Brazil, the prevalence of VaD ranged from 9.3 to 15.9% of dementia cases in population studies conducted in São Paulo state [22–24]. Studies evaluating differences between regions with different degrees of urbanization reported controversial results. The overall prevalence of dementia in rural areas of China was significantly higher than in urban areas (6.05% vs. 4.40%, $P < 0.001$), but this difference was not observed for VaD (1.28% vs. 1.61%, $P = 0.166$) [25]. Other authors, however, suggested that living in rural areas would double the odds of developing VAD (odds-ratio = 2.03) [26].

Comorbidity between AD and vascular brain lesions seems frequent. *Post-mortem* studies indicated that 34% of individuals who presented pathological brain markers of AD also suffered from vascular brain changes [27]. Likewise, another article showed that significant vascular abnormalities occurred in 89% of cases of AD [28]. A population study reported that 40% of patients with dementia presented a combination of AD-related and vascular brain alterations [4]. However, few studies to date have evaluated the prevalence of mixed dementia. A study showed that 12.6% of dementia cases met diagnostic criteria for both AD and VaD [29].

Studies measuring the influence of gender on the prevalence of VaD also produced conflicting results. Moreover, systemic arterial hypertension may double the risk for VaD in females, but not in males, while physical exercises appear to protect women more efficiently than men from VaD [26].

Studies on the incidence of VaD are rare and conflicting in the literature. According to North American data, VaD, with or without associated AD component, has an annual incidence of 14.6 per 1000 people for Caucasians and 27.2 per 1000 people for African Americans [30]. According to studies, the incidence rates of VaD did not differ between men and women [27].

3. Classification and diagnosis

3.1 Subtypes and clinical criterium

Cognitive alterations due to cerebrovascular disease (CVD) have been classified within a continuum named Vascular Cognitive Impairment (VCI), and the term VaD is currently reserved for the stages in which such deficits reach dementia severity [2, 31]. The concept of VCI involves presymptomatic presentations with high risk for cerebrovascular disease ("brain-at-risk"), as well as cases of cognitive impairment of vascular etiology that do not meet criteria for VaD, referred to as Vascular Cognitive Impairment No-Dementia (V-CIND) or Vascular Mild Cognitive Impairment (VaMCI) [6, 32].

VCI encompasses a combination of various types of cerebral vascular lesions, i.e., multiple cortical or subcortical infarctions, strategic infarctions, microangiopathic lesions of white matter, base nuclei hypoperfusion lesions, and hemorrhagic lesions [31]. As a result of the array of pathological processes leading to parenchymal damage, heterogeneous clinical presentations, including motor, cognitive and neuropsychiatric manifestations, could be identified. Hence, to enable a didactic approach to these conditions, some authors have sought to define VCI subsyndromes based on the mechanism of vascular brain injury, which generated the concepts of "dementia by multiple infarctions," "dementia by strategic infarction," and "vascular dementia by subcortical ischemia."

Dementia due to multiple infarctions results from disease of the large cerebral vessels, resulting mainly from vascular thromboembolism. Cortico-subcortical infarctions of variable extension are observed [33]. Symptoms typically start abruptly and evolve in a stepwise pattern, succeeding ischemic brain events. With the accumulation of brain lesions, the patient begins to develop focal neurological signs, such as asymmetric reflexes, pseudobulbar syndrome (i.e., difficulties swallowing and speaking, in addition to effective lability), the release of primitive reflexes (such as Babinski reflex), and sensory abnormalities [33].

Dementia by strategic infarction is understood as a single lesion (or few lesions), which occurs in a functionally important location. It may result from cortical or subcortical infarction, whether unilateral or bilateral. Examples are dementias resulting from thalamic or hippocampal infarction [33].

Dementia due to subcortical ischemic vascular disease (SIVD) is the most frequent subtype of VaD, and it is associated with changes in small cerebral vessels (perforating arteries) disease, secondary mainly to hypertensive arteriopathy. It covers two clinical subsyndromes: Binswanger disease and lacunar state. Binswanger disease consists of dementia due to large subcortical infarctions, while in lacunar infarcts, multiple punctiform or rounded lesions are observed in the cerebral parenchyma. The clinical picture is usually insidious in most cases.

VaD due to subcortical ischemia may also be associated with the presence of a mutation in the NOTCH3 gene, of autosomal dominant transmission, causing the disease known by the acronym CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). This disorder presents as VaD by multiple subcortical infarctions of presenile onset. Symptoms include, in addition to severe cognitive deficits, the presence of migraine with aura, mood swings, and apathy.

The most used diagnostic guidelines for the detection of VaD are summarized in **Table 2**. Except for Hachinski's Ischemic Score (HIS), based solely on clinical criteria, the diagnosis of VAD depends on the demonstration of cognitive deficits through neuropsychological testing and the relationship between cognitive impairment and the vascular brain alterations identified to neuroimaging. The definition of dementia varies according to the criteria employed, leading to difficulties interpreting the results of studies that use different diagnostic systems.

3.2 Historical evolution of the VCI concept

Although the evolution of knowledge about the clinical and neuroimaging characteristics of VCI has led to the improvement of diagnostic guidelines, some questions remain. The HIS, elaborated in 1975, was one of the first instruments to suggest a differentiation between "dementia by multiple vascular infarctions" and "primary degenerative dementia" through clinical criteria. Among them, the items "abrupt onset" and "stepwise evolution" refer to the pattern of cognitive deficits that follow episodes of vascular ischemia (e.g., vascular brain ictus). Following this principle,

Diagnostic criteria	EIH (1975)	ADDTC (1992)	CID-10 (1992)	NINDS-AIREN (1993)	ASA/AHA (2011)	DSM-5 (2013)
Clinical criteria	Abrupt onset, "stepwise" evolution, fluctuation, nocturnal confusion, personality preservation, depression, somatic complaints, emotional lability, arterial hypertension, history of stroke, focal symptoms, focal signs, other signs of arteriosclerosis	Cognitive decline in more than one domain, CVD (demonstrated by a history of two or more vascular events, focal neurological signs, or one stroke with a clear temporal relationship with cognitive alterations), functional impairment, high HIS, history of TIAs, history of risk factors for CVD (hypertension, diabetes, heart disease)	Impairment of memory and intellectual activities (thinking, reasoning, and flow of ideas), with consequent functional impairment, absence of disturbance of consciousness, deterioration of emotional control, social behavior and motivation, focal neurological signs, deficits present for at least six months.	Memory impairment +1 other cognitive domain, functional impairment, focal signs, the onset of dementia up to 3 months after stroke, abrupt onset, fluctuating course or "stepwise progression," other signs suggestive of CVD (gait disorders, falls, change in urinary frequency or urgency, pseudobulbar paralysis, abulia, depression, emotional incontinence, psychomotor retardation, executive dysfunction)	Impairment in two or more cognitive domains demonstrated by tests, functional impairment; a clear temporal relationship between deficits and vascular event or a clear relationship between severity and pattern of cognitive impairment; the presence of subcortical and diffuse CVD, absence of progressive evolution of deficits suggestive of neurodegenerative disorder	The onset of symptoms related to one or more vascular brain events, evidence of a more prominent decline in attention (including processing speed) and executive function, CVD by history, physical examination, and neuroimaging
Laboratory criteria/ neuroimaging	—	Evidence of 2 or more areas of vascular lesions at neuroimaging, evidence of at least one vascular lesion (in non-cerebellar location), presence of multiple infarctions	Presence of cortical, subcortical, or mixed infarctions	Evidence of CVD to neuroimaging, two or more ischemic events, severe territorial, strategic, or subcortical infarction	Evidence of CVD to neuroimaging	Evidence of CVD to a degree sufficient to cause cognitive symptoms, significant brain parenchyma injury, genetic evidence of CVD

Table 2.
Diagnostic criteria for vascular dementia.

more recent diagnostic guidelines require a temporal relationship between vascular events and cognitive impairment. However, recognizing subcortical ischemic disease as a cause of dementia of insidious evolution makes it necessary to adapt the criteria for the best detection of this type of condition. In addition, the memory impairment requirement, present in ICD-10 and NINDS-AIREN, derives from an approximation between VaD and more specific cognitive attributes of AD. The DSM-5, published in 2013, has brought advances in this aspect, highlighting the presence of compromises in attention, processing speed, and executive function. Another data that deserves attention is the inaccuracy of neuroimaging criteria since the extent of white matter lesions necessary to generate cognitive alterations with dementia severity is not defined by the classification systems. Finally, the requirement of deficits in at least two domains is consensual among the most recent diagnostic guidelines. However, the cut-off point for cognitive impairment is not established. The National Institutes of Health (NIH) defined the cognitive impairment due to dementia as a cognitive performance of two standard deviations below normative data in at least two cognitive domains, albeit further studies are needed to evaluate the validity of these criteria.

Predementia cognitive alterations of vascular etiology began to draw the attention of researchers in the late 1990s when Bowler's studies warned of the importance of an early diagnosis for VCI [31]. Although the authors already pointed to the need for new diagnostic criteria that included the initial stages of the condition, early studies with Mild Cognitive Impairment (MCI) sought their similarities with AD [34]. In 2003, a study group meeting in Stockholm expanded the concept of MCI to include the "non-amnesic" form of the disorder in the diagnostic criteria [34]. Petersen's diagnostic guidelines published in 2004 placed the MCI as a risk factor for dementia of different etiologies. In vascular conditions, amnestic or non-amnestic MCI with multi-domain involvement would tend to progress to VaD [34]. However, this initial model only included cognitive and functional aspects, not defining neuroimaging criteria for the condition. In 2011, the diagnostic criteria for VMCI were published, developed by the American Heart Association and the American Stroke Association, inspired by the algorithm for detecting VaD proposed by these same entities [6]. The Vascular Cognitive Impairment No-Dementia (VCIND) construct is a more comprehensive concept than the VMCI, since it encompasses a wide range of conditions affecting cognition in the late life, including focal cognitive deficits, genetic disorders, and cognitive alterations secondary to psychiatric disorders. However, a review of the concept of VCIND, proposed by Zhao et al. restricted this construct to bring it closer to the concept of VMCI [35]. The DSM-5 established the diagnostic guidelines for the Mild Neurocognitive Disorder of vascular etiology, defining it as the presence of subtle cognitive impairments due to cerebrovascular disease [36].

Dementia associated with multiple mechanisms of brain damage, such as vascular-related and neurodegenerative processes, has been classified as Mixed Dementia (MD). Despite its increasing prevalence, the concept of MD lacks a clear definition. The HIS conceptualizes MD as an intermediate clinical state with both VaD and AD characteristics [33]. The NINDS-AIREN (1993) did not establish diagnostic criteria for DM, recommending the term "AD + Cerebrovascular disease" [37]. ICD-10 proposed that the diagnosis of MD should be established if the subject fulfilled the criteria for both AD and VaD [38]. The DSM-5 does not present a diagnosis characterization of DM but indicates the possibility of a simultaneous diagnosis of VAD and AD [36].

In addition, diagnostic definitions of VCI generally require observing cognitive dysfunction, vascular risk factors, vascular brain lesions, and focal neurological findings [39]. A classic presentation with stepwise evolution can be found in large-vessel disease [33]. **Table 3** summarizes these aspects.

	Risk and etiological factors	Age of onset	Neuroimaging	Clinical features
Multi-infarct	Hypertension, heart disease, diabetes, coronary disease	From the 4th decade	Cortical lesions and/or white matter and basal ganglia; commitment of the anterior, posterior and middle cerebral arteries	Executive dysfunction, apathy, impairment in attention depression, psychomotor slowing
CADASIL	Mutation of the NOCHT 3 gene	3–4th decades	Hyperintensities in the temporal subcortical region	Migraine, executive dysfunction, family history
Binswanger	Age, hypertension, diabetes	Between 4 and 7th decades	Extensive and diffuse lesions in the subcortical region	Insidious progression, mood swings, psychomotor slowing apathy, motor changes
Lacunar infarctions	Cardiac arrhythmias (atrial fibrillation), heart disease, hypertension	From the 4th decade. Present in up to 30% of individuals over 30 years of age	Lesions in areas adjacent to the lateral ventricles, basal ganglia, thalamus, inner capsule, bridge, and cerebellum	"Silent infarctions"; the presence of risk factors, varied clinical and related to the topography of lesions.

Table 3.
Clinical and radiological features of VaD.

4. Pathophysiology

4.1 Cardiovascular aspects related to VaD

Hypoperfusion related to atherosclerosis and arterial sclerosis, hypotension associated with reduced cholinergic activity, altered autonomic regulation, cortical hypometabolism, disruption of the neurovascular unit, and cardiovascular events such as congestive heart failure, with consequent systolic dysfunction and embolism is among the main events related to cerebrovascular disease and cognitive decline [6, 40]. Vascular lesions may cause impairment in cholinergic function and disconnection of frontal limbic associative fibers. Cholinergic tracts integrate different brain areas, participating in vasomotor control and cognitive and behavioral modulation [33].

SIVD is commonly observed in MRI in the form of subcortical hyperintensities. It results from the interplay of multiple risk factors affecting cerebral small vessels, such as dyslipidemia, hypertension, heart disease, genetics, and diabetes mellitus. Microstructural abnormalities usually comprise gliosis, demyelination, and axonal damage of subcortical connections. White matter lesions, known as leukoaraiosis, may be related to apathy, executive dysfunction, depression, motor alterations, and urinary control and have been considered a reliable predictor for progression to dementia [41]. Studies have shown that extensive white matter lesions, characterized by a score equal to 3 on the Fazekas visual scale, may have a death or disability rate of 29.5%. On the other hand, the identification of leukoaraiosis at MRI may not be exclusively suggestive of SIVD. Additional pathological processes, including inflammation (e.g., multiple sclerosis and neurosarcoidosis), autoimmune diseases (celiac disease), and inherited metabolism errors (leukodystrophy), may appear hyperintense at neuroimaging.

Metabolic	Cardiovascular	Lifestyle	Others
High cholesterol	Arterial hypertension	Tobacco smoking	Psychological stress
Diabetes mellitus	Arteriosclerosis	Alcoholism	Depression
Metabolic syndrome	Atrial fibrillation	Sedentarism	Sleep apnea
High homocysteine	Coronary disease	Inadequate diet	Low education
Obesity	Carotid stenosis		Heart surgery
	Myocardial inflammation		Vasculitis
	Valvulopathy		
	Patent foramen ovale		

Table 4.
Modifiable vascular risk factors.

Cognitive impairment resulting from SIVD may increase the risk for conversion into dementia and directly cause cognitive decline. Executive dysfunction, attention deficit, processing slowing, and visuospatial alterations are frequently observed [36]. Memory impairment tends to be less severe than AD, as it mainly affects free recall and usually spares recognition, and patients can benefit from clues. Apathy, depression, and anxiety are standard features of SIVD. Possibly, a relationship between the extent of the lesions and the location exists with the severity of dementia.

Binswanger disease is characterized as damage of 25% or more of the subcortical region [42]. It is characterized pathologically by thickening the walls of the small arteries with fibrinoid necrosis of large caliber brain vessels [43].

4.2 Vascular risk factors

Vascular risk factors (VRF) encompass disorders with an increased chance of developing brain vessel pathology and circulatory disorders, with eventual nervous tissue damage (CVD), leading to CCV14 [44].

The VRF comprises various causes (genetic, metabolic, cardiovascular, lifestyle, others) underlying the vascular pathology and eventually the nervous tissue supplied by the vascular territory. They can be divided into non-modifiable, currently without adequate treatment or prevention (e.g., genetic [cerebral amyloid angiopathy, CADASIL, Fabry disease]) and modifiable, i.e., amenable to treatment and prevention (e.g., metabolic, cardiovascular) [45–47] (**Table 4**). The various VRF, including genetic diseases, and vascular pathologies, such as embolisms, cerebral blood flow, and perfusional changes, must be considered.

5. Diagnosis

5.1 Clinical evaluation and complementary exams

Anamnesis should investigate vascular risk factors, including arterial hypertension, dyslipidemia, diabetes mellitus, and sickle cell anemia [33]. Previous personal or familial history of vascular brain events should be characterized. Lifestyle habits, including alcohol and tobacco consumption and unhealthy diet, are strongly associated with VCI.

Clinical evaluation should also be directed to screening cognitive symptoms, especially to difficulties for goal-directed behaviors and sustained attention, as well as for deficits in cognitive speed [36]. Other abnormalities may include problems remembering recent events, difficulties organizing the personal agenda and planning tasks, reduced verbal fluency, and impaired spatial orientation.

Behavioral changes, either sudden or insidious, such as irritability, reduced general interest, and social isolation, often indicate depressive symptoms. In addition, personality changes, visible in social situations where the behavioral pattern is beyond the usual, may denote changes in brain function. A third component aspect of anamnesis is functional assessment, which addresses the degree of autonomy for resolving indoor or outdoor tasks, such as making a meal, paying bills, or dealing with money. For greater diagnostic accuracy, it is always desirable to have a companion throughout the examination, preferably those with recurrent or continuous contact, considering the possibility of cognitive impairment in the patient.

The detailed neurological clinical examination should be guided by investigating comorbidities such as hypertension, atrial fibrillation, dehydration, infection, delirium, number of prescribed medications, alteration of sphincter control, motor difficulties or speech articulation, the occurrence of falls, as sudden changes in the level of consciousness.

5.2 Neuropsychological assessment

The neuropsychological and clinical characteristics of VaD vary depending on the location and extent of the lesions. Neuropsychological evaluation analyzes the repercussions of brain lesions and dysfunctions on the cognition and behavior of the patient [48]. The differential diagnosis of AD and VaD, the most frequent types of dementia, can be challenging; as previously mentioned, those two pathological processes may share similar clinical characteristics, and they may co-occur [1]. In addition, neuropsychological evaluation may help assess clinical status, contributing to planning therapeutic strategies and family guidance [49]. Some of the main findings on neuropsychological differences in the most homogeneous group of SIVD and AD are summarized in **Table 5**.

5.3 Neuroimaging assessment

Different guidelines recommend the use of neuroimaging for the characterization of cerebrovascular disease [6, 39, 50–53]. Initially, as proposed by the National Institute of Neurological Disorders and Stroke–Canadian Stroke Network in 2006, these methods were recommended solely in research settings [50]. In 2011, with the American Heart Association/American Stroke Association recommendations, neuroimaging became a critical diagnostic tool in clinical practice [6].

Cognitive function	SIVD	AD
Memory	• Minor impairment of episodic memory; Relative preservation of recognition memory, with benefit in the face of recognition clues	• Marked impairment in episodic memory (immediate memory and evocation); little benefit in the face of recognition clues
Language	• More significant impairment in phonemic verbal fluency; • Lower frequency of naming errors	• More significant impairment in semantic verbal fluency; • Higher frequency of naming errors
Executive functions	• Marked impairment in planning tests, "sequencing," cognitive flexibility, and alternating attention; • Impairment in psychomotor speed	• Improved performance in executive function tests and psychomotor speed

Table 5.
Differential diagnosis of VAD and AD according to cognition.

5.3.1 Structural brain neuroimaging

Computed tomography (CT) is sufficient to rule out other causes of cognitive decline besides VCI, such as tumor processes, subdural hematoma, or hydrocephalus. Lacunar infarctions and, to a lesser extent, subcortical lesions can be seen on CT. The detection of vascular brain disease by magnetic resonance imaging (MRI) is made through T2 and Flair-weighted images (**Figures 1** and **2**), the latter being the preferred sequence for identifying subcortical hyperintensities. In the case of thalamic strategic infarctions, the T2 sequence can contribute to its more precise location. Micro bleeds and calcifications may be better detected with the use of T2-weighted images. The finding of watershed infarcts between the anterior and middle cerebral artery is usually seen in the dominant hemisphere, in the case of anterior cerebral artery flow territories, bilaterally, preferably by FLAIR sequences.

The presence of lesions suggestive of ischemia or lacunar infarction on MRI or tomography should always be correlated with clinical examination and neuropsychological examination findings. On the other hand, the absence of vascular lesions on CT or MRI indicates the low probability of a vascular etiology of dementia. The operational guidelines of the NINDS-AIREN - Association Internationale pour la Recherche et l'Enseignement en Neurosciences - are used to understand the radiological aspects of VCI, being fundamental for the diagnosis of probable VaD [33, 37].

Subcortical vascular lesions result from small vessel disease and can be identified at MRI as pointy, diffuse, or localized areas, hyperintense in FLAIR and T2-weighted sequences [53]. Some authors distinguished their locations in periventricular and subcortical. Several studies in neuroimaging have adopted volumetric techniques for the measurement of neuroimaging volume. However, visual methods have wide use in the clinical routine, giving their straightforward interpretation an advantage. One is the use of the Fazekas scale (**Figure 1**), ranging from 0 to 3. Recommendations for neuroimaging characterization of SIVD also include the analyses of cerebral microbleeds and perivascular spaces [39, 50, 53].

Diffusion tensor or diffusion tensor imaging (DTI) is a structural resonance technique based on the displacement of water molecules along axon fibers. DTI can be very useful as a biological marker of loss of axonal integrity and is a promising technique in the early diagnosis of neuronal disconnections in several neuropsychiatric conditions, including VAD. Studies investigating brain vascular-related changes have shown the importance of evaluating specific brain regions, such as

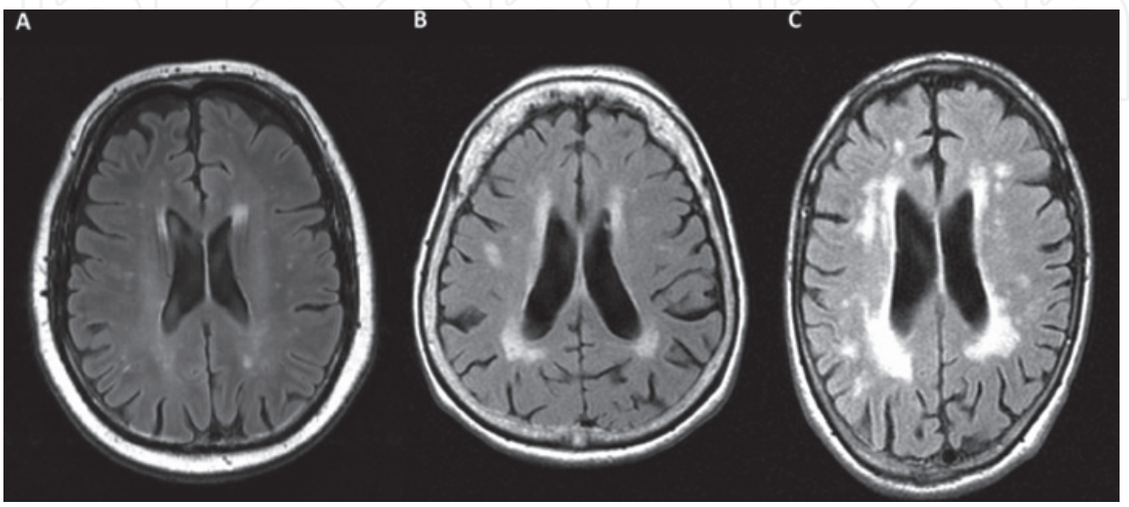

Figure 1.
The proportion of white matter hyperintensities to magnetic resonance imaging with FLAIR sequence. The score on the Visual Scale of Fazekas for light (A), moderate (B), and advanced (C) levels were corresponding to the score of 1, 2, and 3, respectively.

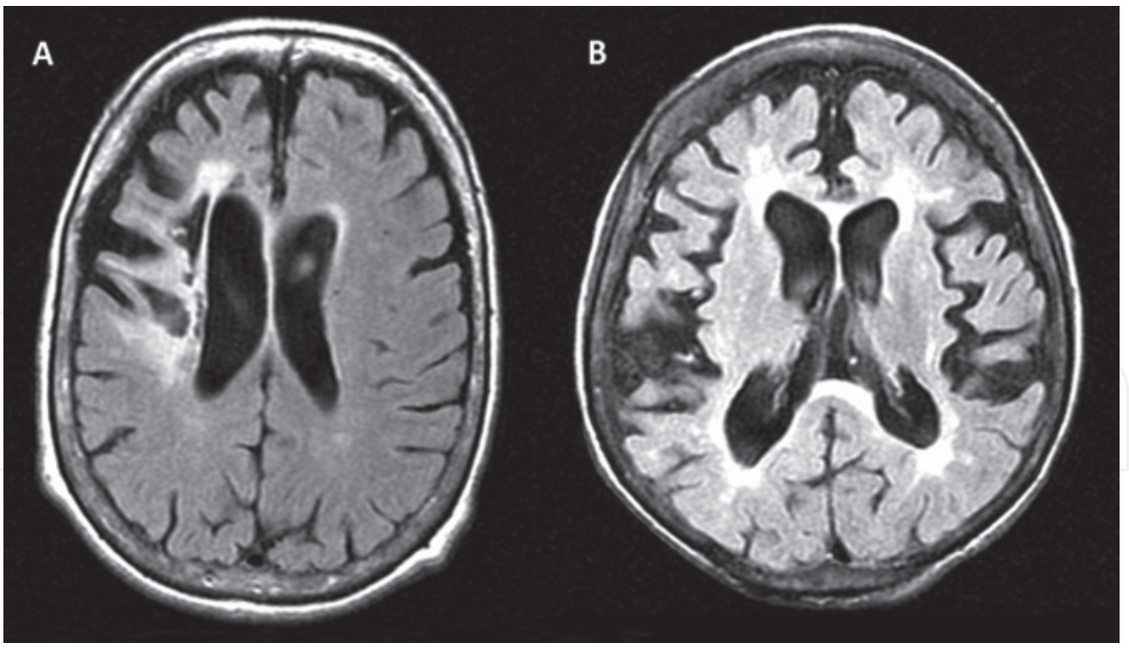

Figure 2.
Flair image (A) shows cortico-subcortical infarction on the right, corresponding to the anterior cerebral artery territory with caudate nucleus injury. In some individuals, extensive white matter injury correlates with more significant overall cortical atrophy and increased risk for dementia, as shown in image (B).

fornix, cingulate, and hippocampus; another focus of clinical interest of DTI has been the investigation between vascular and degenerative factors in dementia, especially the role of ischemic vascular lesions in conversion to AD [54]. In addition, axonal lesions may be associated with increased blood pressure, even in the absence of a diagnosis of hypertension [55].

5.3.2 Structural imaging in peripheric vascular disease

Neurovascular evaluation includes several complementary tests, such as ultrasonography (USG) of cervical carotid and vertebral arteries and CT or RM angiography of the carotid and vertebral arteries. These tests investigate vascular pathologies, e.g., atheromatous plaques and changes in cerebral blood flow. In cases where detailed visualization of the cervical and intracranial arterial tree is necessary, such as suspected aneurysm, MRI or CT angiography may be used.

5.3.3 Perfusion and molecular methods

The use of single-photon emission tomography (SPECT) seems relevant in the differential diagnosis with VAD and, in typical Binswanger-type VaD, the finding of diffuse hypoperfusion. Concerning positron emission tomography (PET), different patterns of metabolism reduction are usually associated with VAD; these include diffuse hypometabolism in SIVD, frontal or multifocal, as in the case of lacunar or multiple infarctions. The use of PET or SPECT is recommended in the investigation of atypical cases, in which there are doubt diagnoses after clinical examination and structural neuroimaging.

5.4 Behavioral assessment

The comorbidity of VCI and mood disturbances, particularly affective symptoms, led to the proposition of a hypothesis known as "vascular depression" [56]. Statistically, anxiety (70%) and depression (20%) are the most frequent symptoms

found in VCI [57]. Studies estimate that the prevalence of depression in VaD is 13.1% in community samples and 21.4% in-hospital samples [57]. The high prevalence of depression in VAD (8–66%) and the frequent occurrence of visual hallucinations, especially in multi-infarct dementia, were observed compared to AD [58]. Conversely, mania (1%), psychotic symptoms are less common but have frequency similar to that encountered in AD.

The neuropathological mechanisms associated with behavioral alterations result from frontal and or subcortical involvement in different circuits and may reflect diffuse lesions or strategic anatomical structures. Behavioral changes may be accompanied by cognitive symptoms, such as concentration difficulties, slowing cognitive processing, and executive dysfunction.

6. Treatment principles

6.1 General principles of treatment

Considering the absence of specific treatment of CCV, the available therapeutic strategies comprise, above all, aspects of prevention [45, 59]. Therefore, the binomial control of risk factors—promotion of good health constitutes the main objective from the individual, epidemiological and public health point of view. Successful prevention depends on the control and modification of risk factors and the effectiveness of protective factors, such as adequate lifestyle (including diet, physical activity, among others) [46]. It should be emphasized that prevention measures should be maintained from the brain-at-risk to the various CCV symptomatic presentations.

Neuropsychiatric symptoms are seen in all phases of CCV, most marked in the more advanced ones. Its treatment is necessary, considering its interference in other areas of performance and the quality of life of patients and family members. Treatment can be established after the correct definition of the problem, away from personal environmental factors of discomfort, and the differential diagnosis (e.g., delirium [infectious, metabolic, or drug-induced confusional states]). Initially, non-pharmacological strategies (environmental, behavioral, psychological, should be used) and pharmacological treatment, when indicated, should be safe and effective, minimizing cardiovascular side effects to avoid additional vascular injury [60].

The treatment of VaD can be didactically divided into pharmacological and non-pharmacological strategies. The first includes preventive measures based on epidemiological findings, e.g., the effective control of vascular risk factors [61]. Therefore, there is consensus among the authors regarding the need to treat hypertension, dyslipidemia, diabetes, and other associated factors, although the effect size of preventive, therapeutic interventions for each risk factor remains disputable [6]. Nevertheless, studies suggest that effective control of hypertension results in a decrease of up to 34% in the incidence of VaD.

6.2 Non-pharmacological treatment

6.2.1 Control of cardiovascular and metabolic risk factors

Both hypertension and diabetes and have been related to the higher incidence of VCI. Blood glucose control should be moderate (glycated hemoglobin between 7 and 7.9%); however, scarce evidence for a specific class of antihypertensive drugs remains [6, 62]. Patients with heart disease, e.g., atrial fibrillation, should be carefully monitored for appropriate anticoagulation levels. Smoking cessation should be stimulated regardless of age group.

6.2.2 Physical exercise

Evidence from animal studies points to the benefits of physical activity in angiogenesis, brain, and neurogenesis. Population studies have confirmed these findings by demonstrating a favorable role of physical activity in the lowest conversion rate for dementia and the most beneficial evolution [6]. However, the benefits seem less robust for VaD than for AD [6].

6.2.3 Diet and supplementation

The higher intake of polyunsaturated acids and omega 3, fibers, bowls of cereal, the moderate consumption of milk and its derivatives, meats, and saturated fatty acids have been associated with reducing the conversion of MCI and AD. Moderate alcohol use in about one or two drinks (<30 g/d) and adequate weight control also had a protective effect on VAD development. The mechanisms underlying this effect would be reducing LDL, increased HDL, reducing alcohol consumption, insulin resistance and blood pressure, reducing platelet aggregation and serum fibrinogen and homocysteine levels and inflammatory markers.

6.2.4 Neuropsychological rehabilitation

Neuropsychological rehabilitation may have a role in the treatment of cognitive deficits and neuropsychiatric symptoms in VCI. Individual or group family support can also be valuable in the rehabilitation process, providing caretakers with information about the disease and prognosis and offering emotional support for coping [63]. Most studies with cognitive intervention, however, showed reduced efficacy in improving cognitive function with cognitive rehabilitation. Some findings highlight the lack of evidence due to methodological difficulties, such as the duration of the intervention, the instruments used as the control of confounding variables (medical comorbidities and psychiatric alterations).

6.3 Pharmacological treatment

6.3.1 The use of cholinesterase inhibitors

The frequent overlap of pathological mechanisms between VaD and AD suggests that the use of acetylcholinesterase inhibitors may be useful in patients with vascular brain disease. The use of donepezil showed good tolerability and may improve cognitive and functional status. Rivastigmine has shown to be effective on cognition, although with an effect size proportionally lower than donepezil [62].

The use of cholinesterase inhibitors and the N-methyl-D-aspartate (NMDA) receptor modulators in patients with VaD and VCI has been controversial, although the benefits seem more evident with specific groups, e.g., individuals with the subcortical disease. Memantine, an NMDA antagonist, would act on the toxic action caused by glutamatergic overactivation, putatively exhibiting brain neuroprotective properties. There is also a need for further evidence demonstrating the benefits of this medication in VAD, but some specialists point to a possible improvement in subcortical conditions [62].

6.3.2 Treatment of behavioral changes in VCI

Pharmacological treatment of behavioral alterations aims at symptomatic remission or stabilization. Antidepressants may be indicated in moderate or severe

depressive symptoms or when monotherapy with acetylcholinesterase inhibitors has no effective response. Serotonin reuptake inhibitors (SSRI), venlafaxine, mirtazapine, and trazodone are usually regarded as the safest and most well-tolerated options.

The use of trazodone or anticonvulsant has been used in maniform symptoms, agitation, or aggressive behavior. Carbamazepine shows evidence of success in reducing agitation. Newer drugs such as gabapentin may still show effectiveness in these conditions. Atypical antipsychotics may also be an alternative in agitation, and use should be restricted to the acute period. Risperidone and olanzapine are drugs with better tolerability. However, the occurrence of sedation and risk and falls and the evidence of increased incidence of drug-related vascular events demand thorough dosage monitoring, with the risks and benefits being weighed on a case-by-case basis.

6.3.3 Alternative treatments

The use of ginkgo Biloba, nimodipine (potassium channel blocker), and antioxidant agents requires further scientific evidence.

Regarding surgical interventions, studies have sought evidence of improvement in cognitive function after carotid revascularization, but the results are still inconclusive. Conversely, studies have pointed to cognitive improvement after carotid stent implantation against embolism, but these results require confirmation with long-term follow-up of patients.

7. Conclusion

This chapter provided a concise review of epidemiological, diagnostic, and clinical aspects of vascular brain diseases. For most countries, vascular brain disease is a significant cause of dementia, and their presence, alone or associated with degenerative conditions, increases the risk of conversion to progressive cognitive decline. Neuropsychiatric manifestations vary according to the affected brain territory and disrupted neuronal circuits; behavioral disturbances include, for instance, mood, psychomotor, or thought disorders; cognitive deficits involve memory, attention, language, and other alterations, depending on the extension and localization of the lesions. Early diagnosis may have a decisive impact on clinical evolution and should guide health policies involving the old age population. Treatment involves a wide range of strategies, including controlling cardiovascular and metabolic risk factors and adopting a healthy lifestyle. Pharmacological treatment may include cholinesterase inhibitors and NMDA modulators, which aim to stabilize symptoms and, although not officially approved, are recommended depending on the stages of dementia. The safety and effectiveness of antipsychotics and antidepressants, particularly in managing agitation, psychosis, and depression, require further studies.

Conflict of interests

The authors declare no conflict of interests.

Abbreviations

AD	Alzheimer's dementia
TIA	transient ischemic attack
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

CVD	cerebrovascular disorders
DTI	diffusion tensor imaging
HIS	Hachinski ischemic scale
HIE	hemorrhagic ischemic events
ICD	international classification of diseases
MCI	mild cognitive impairment
MD	mixed dementia
NINDS-AIREN	Association Internationale pour la Recherche et l'Enseignement en Neurosciences
NMDA	N-methyl-D-aspartate
VaD	vascular dementia
VCI	vascular cognitive impairment
VCIND	vascular cognitive impairment not dementia
VMCI	mild cognitive impairment of vascular origin
VRF	vascular risk factors
SIVD	subcortical vascular ischemic disease
SPECT	single-photon emission tomography

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