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AN OVERVIEW OF VASCULAR DEMENTIAS: THEIR CHARACTERISTICS AND CHALLENGES FOR THE CORRECT DIAGNOSIS AND TREATMENT

Emir Nunes Piauilino
Faculdade de Medicina ITPAC Santa Inês
Santa Inês - MA
http://lattes.cnpq.br/9411489070558508

Maysa Jacqueline Vale Pereira
Faculdade de Medicina ITPAC Santa Inês
Santa Inês - MA
http://lattes.cnpq.br/7124411311971336

Vitor de Jesus Costa Barros
Faculdade de Medicina ITPAC Santa Inês
Santa Inês - MA
http://lattes.cnpq.br/6303618483952691

Abstract: Dementias are currently classified mainly as Vascular Dementia (DV) and Alzheimer's Disease (AD), the latter being the most prevalent worldwide and the main differential diagnosis of the former, since some of its pathophysiological mechanisms, as well as their clinical presentations are congruent. In this sense, the pathophysiological mechanisms, the clinical, laboratory and radiological characteristics of VD are of fundamental importance for the correct diagnosis and, consequently, for the adequate treatment, which has peculiarities of great relevance. In general, VD is related to factors that somehow lead to vascular insufficiency, impairing perfusion in specific areas of the brain, thus causing the most diverse types of deficits, including cognition, memory, behavior, somatic control, among others. others. The diagnostic challenge for dementias, especially for VD, remains in the scientific community. Due to the high prevalence and incidence of the disease, new means are sought every day to achieve an accurate and early diagnosis.
Keywords: Vascular Dementia; Alzheimer's disease; Insanity; Neurodegenerative Diseases; Degenerative Diseases of the Nervous System;

DEFINITION AND EPIDEMIOLOGY

Dementias correspond to a series of cognitive disorders that lead to a progressive decline in brain functioning, affecting judgment, memory, language and others (BARLOW, 2009). They result from the association of genetic and environmental factors, varying with time, age and individual physiology, occurring more frequently in the elderly. There is a higher prevalence among women and the risk of developing dementia doubles every five years from the age of 65 (BARLOW, 2009).

They correspond to one of the greatest global challenges for health and social assistance in this century. It is the fifth largest contributor to the global burden of disease, with an annual global economic cost exceeding $1 trillion in 2018. More than 50 million people worldwide suffer from dementia, and this number is expected to triple by 2050 (ROMAY MC, et al., 2019; MOROVIC S, et al., 2019; GRANDE G, et al., 2020).

The two most common types of dementia are Alzheimer's disease (AD), accounting for 50 to 60% of cases, followed by Vascular Dementia (DV) with approximately 30% of cases (WHO, 2019). However, the coexistence of vascular pathology in patients with Alzheimer's or other neurodegenerative processes suggests that the true contribution of vascular mechanisms to dementia is significantly greater (ROMAY MC, et al., 2019). It is also estimated that in these first decades of the XXI, about 40% of patients with dementia have chronic cerebral ischemia (LI C, et al., 2021).

As observed in the graph below (Figure 1), AD was more prevalent than DV in all regions surveyed, with emphasis on the South American study (Brazil), which presented a result 2 to 3 times higher than the other regions. An important reversal of this relationship occurred in 30% of the Asian studies, with the prevalence of VD reported in two studies (Park J, et al, 1994; Komahashi T, et al, 1994) as 2 times higher than that of AD. The effect of age on these two etiological diagnoses could also be observed when verifying that there was a significant increase in the AD/DV ratio in centenarians. (LOPES, Marcos A.; BOTTINO, 2002)

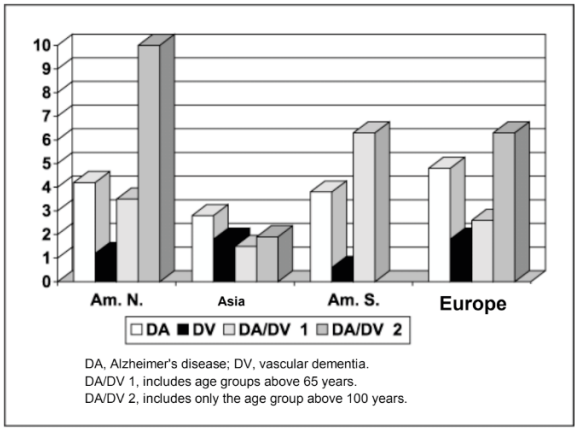

Figure 1: Distribution of types of dementia in different continents.

Source: https://doi.org/10.1590/S0004-282X2002000100012

Vascular Dementia, despite being considered the second most common cause of dementia in Caucasian populations, may be the most common cause in East Asian populations (IADECOLA, et al. 2019). There are few recent epidemiological data on subtypes of dementia, in part due to classification difficulties: mixed neurodegenerative and cerebrovascular pathology is common and, in fact, is present in most elderly individuals (> 75 years) who die with dementia. al. 2018). Some studies have pointed to the incidence of new cases of Vascular Dementia at 6 to 12 cases per 1,000 people over 70 years old (NGUYEN DH, et al., 2021).

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

Different etiologies may be responsible for the development of a dementia syndrome and the differential diagnosis is based on clinical history, laboratory and imaging tests, neurological examination and differentiation of the characteristic profile on neuropsychological assessment (ARAÚJO; NICOLI, 2010).

Although there are different hypotheses for the pathophysiology of AD, its emergence is credited to the progressive accumulation of senile plaques resulting from the deposit of abnormally produced ß-amyloid protein and neurofibrillary tangles, the result of tau protein hyperphosphorylation, which result in neuronal loss and synapses, glial activation and inflammation. This process leads to the death of neurons and consequently brain atrophy. Some areas are more involved in this neurodegenerative process, such as the hippocampus and entorhinal cortex (areas related to memory), with loss of hippocampal volume in the earlier stages of the disease. (Parihar, Hemnani, 2004).

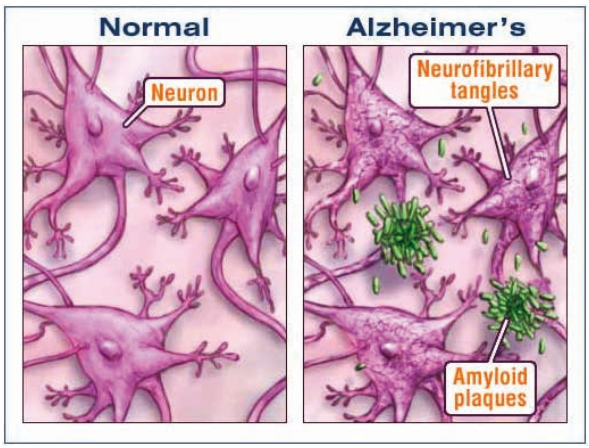

Figure 2: Histological alteration in Alzheimer's disease

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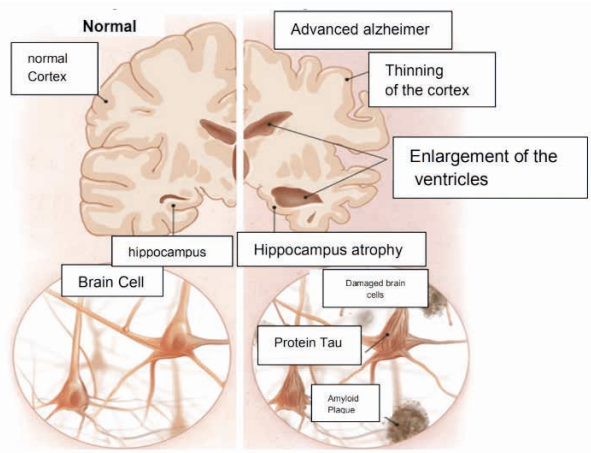

Figure 3: Changes in brain structure in Alzheimer's disease

Source: Doenca-de-Alzheimer-alteracoes-no-cerebro.png

VD is marked by cognitive impairment directly related to vascular injury in the brain, with several known potentially related factors (BIR SC, et al., 2021; WANG XX, et al., 2020; OSBORNE AG, 1994). With regard to vascular risks, there is growing evidence that atherosclerosis, dyslipidemias, diabetes, obesity and hypertension contribute to neurodegeneration and dementia by causing occlusion of an artery or disease of small vessels. Other secondary vascular risk factors, such as late hormone replacement therapy, menopause and preeclampsia, have already been described in the literature (NGUYEN DH, et al., 2021).

Some studies have pointed to a significant number of cases of late-onset dementia attributed to cardiovascular risk factors, such as hypertension, diabetes and obesity, and psychosocial factors, such as education, entertainment, social involvement and leisure activities, which are the main modifiable factors that can be intervention target. An estimated one-third of late-onset dementia can be attributed to seven modifiable risk factors, such as low education, midlife hypertension, midlife obesity, diabetes, physical inactivity, smoking, and depression (Barnes and Yaffe, 2011) and a reduction and prevalence of these risk factors by 10-20% per decade could reduce the worldwide prevalence of AD by 2050 by 8-50% (Baumgart et al. 2015).

In this sense, as the history of previous stroke is directly linked to vascular dementia, the risk factors for stroke are applied to this pathology in the general population. In population-based studies, major risk factors for vascular dementia include: older age, hypertension, diabetes, high levels of total cholesterol, less physical activity, low or high body mass index, smoking, coronary artery disease, and atrial fibrillation (SMITH, et al. 2018).

	Modifiable risk factors (Qiu et al. 2010; Norton et al. 2014; Baumgart et al. 2015)	PAR (95%CI) (Norton et al. 2014)
Cardiovascular risk factors	Diabetes middle age obesity hypertension in middle age Hyperlipidemia	2,9%(1,3-4,7) 2,0%(1,1-3,0) 5,1(1,4-9,9) Inconsistent data/ no definitive data
lifestyle risk factors	Smoke physical inactivity Diet cognitive inactivity	13,9%(3,9-24,7) 12,7%(3,3-24,0) No definitive data No definitive data
Other risk factors	Low education level Traumatic brain injury Depression Sleep disorders	19,1%(12,3-25,6) No definitive data 7,9%(5,3-10,8) Inconsistent data/ no definitive data

Figure 4: Risk factors for vascular dementia

Source: https://doi.org/10.1111/jnc.14132

The heterogeneity of cerebrovascular disease makes it challenging to elucidate the neuropathological components and their mechanisms. Vascular cognitive impairment is an entity whose heterogeneous clinical manifestations are due to a miscellany of pathogenic and structural factors and several biological mechanisms may be related. However, the decrease in cerebral blood flow is the main alteration involved, being directly related to disorders such as atherosclerosis and arterial stenosis (KITAGAWA, 2010; YANG, et al. 2017; SABRI, et al. 2000)

Factors that define subtypes of dementia include the nature and extent of vascular pathologies (such as ischemic infarcts, hemorrhages, and white matter changes), the degree of involvement of extra and intracranial vessels, and the anatomical location of tissue changes. A prospective screening study showed that seven pathologies, including large infarcts, lacunar infarcts, microinfarctions, myelin loss, arteriolosclerosis, leptomeningeal cerebral amyloid angiopathy, and perivascular space dilation, predict cognitive impairment

(SKROBOT, et al. 2016; KIM, et al. 2014; KALARIA, 2016).

The mechanism underlying vascular damage involves a multifactorial process leading to demyelination and gliosis, including disruption of the blood-brain barrier, hypoxia and hypoperfusion, oxidative stress, neuroinflammation and alteration in neurovascular unit coupling, cerebral microhemorrhages or superficial siderosis. al. 2019). At the same time, other causes of vascular dementia described in the literature are arteritis, vasculitis (FRANTELLIZZI, et al. 2018), including local and systemic inflammatory syndromes, subdural or subarachnoid hemorrhage, venous thrombosis/infarcts, infectious vasculitis, hippocampal sclerosis, angiomatous lesions/ tumors disorders and chronic migraine [HOKKANEN, et al. 2017; MANCINI, et al. 2019; KIM, et al. 2015).

VD is generally a sporadic disease from a familial point of view, and it is not usual to find well-defined inheritance patterns. However, there are monogenic forms that must be recognized for an accurate diagnosis and correct family counseling (CIPOLLINI, et al. 2019), such as autosomal dominant cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (KURZ, et al. 2003; TATSCH, et al. 2003; NA, et al. 2003), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) (VERDURA, et al. 2015), and cathepsin A-related arteriopathy with strokes and leukoencephalopathy (CARASAL) (BUGIANI, et al. 2016). Other adult-onset genetic leukoencephalopathies have recently been described, such as diffuse hereditary leukoencephalopathy with spheroids (LYNCH, et al. 2016). Furthermore, it is likely that other pathophysiologic processes play a role in vascular dementia within a mixed pathologic process, including possible interactive injury with Alzheimer's Disease and other neurodegenerative processes (VAN DER FLIER, et al. 2018; KIM, et al. 2013).

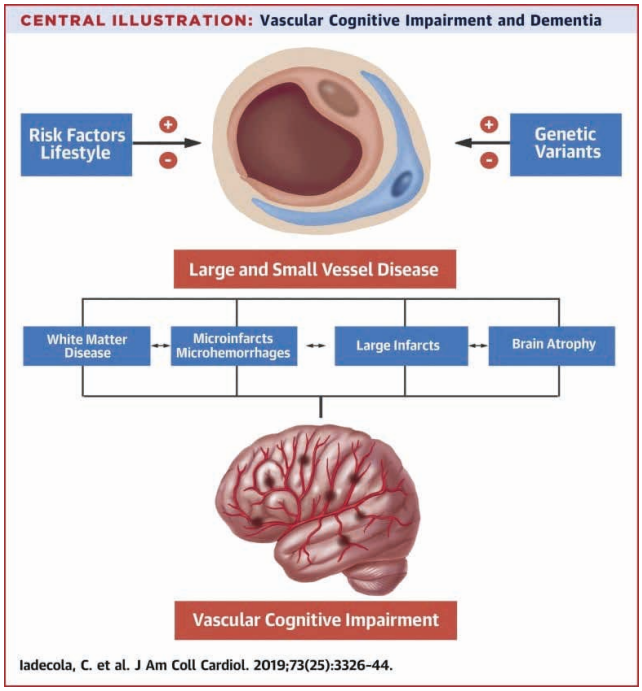

Figure 4 Mechanisms that lead to vascular injury and consequently to the cognitive disorders of VD

Source: https://doi.org/10.1016/j.jacc.2019.04.034

VD is classified into 5 subtypes based on their main causes (VENKAT, et al. 2015):

- Dementia due to multiple infarcts - There are multiple cerebral infarcts, involving cortical and subcortical areas, usually caused by occlusion of large vessels. They have an abrupt onset, rapid progression, pyramidal signs, hemiparesis, hemi-sensory loss, neuropsychological deficits and memory impairment.
- Subcortical vascular dementia (small vessel disease) - can lead to cortical and subcortical lesions and are often observed in the white matter of the elderly brain. This leukoencephalopathy can lead to subcortical dementia syndrome, characterized by memory impairment, abnormal executive

function, psychomotor retardation, euphoria, psychosis, symmetrical hemiparesis, ataxic supranuclear palsy, sphincter incontinence, and parkinsonism (often without tremor). Lacunar infarcts in the basal ganglia, thalamus, and internal capsule characterize the lacunar state, marked by memory impairment, psychomotor retardation, apathy, depression, multifocal motor symptoms, parkinsonism, and pseudobulbar palsy. Multiple frontal white matter infarcts lead to Binswanger's disease, with pseudobulbar signs, abulia, behavioral changes, bilateral pyramidal signs, memory and attention disturbances, psychomotor retardation, gait disturbances, urinary incontinence, and parkinsonism (rigidity, akinesia).

- Demência induzida por AVC - a single major stroke, causing damage to functionally important areas, the symptomatology being defined according to the injured area. Angular gyrus infarcts present with acute aphasia, alexia with agraphia, memory disturbances, spatial disorientation, agnosia, and dyscalculia. Amnesia, psychomotor agitation, visual hallucinations, confusion, agnosia, and visual deficits are common in posterior cerebral artery infarcts. Abulia, transcortical motor aphasia, memory loss, dyspraxia, contralateral hemiparesis, hemi-sensory loss in the lower extremities and sphincter incontinence can be seen in infarcts of the anterior cerebral artery. Middle cerebral artery infarcts lead to severe aphasia, alexia, agraphia, dyscalculia, psychosis, contralateral pyramidal signs, hemiparesis, sensory loss, and visual field deficits. Carotid artery occlusions can lead to aphasia (when they occur in the left hemisphere), visuospatial deficits, contralateral hemiparesis and hemi-sensory loss. Infarcts in the branches that perfuse the thalamic area can lead to aphasia (left side), impaired memory and attention, and variable motor and sensory loss.
- Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)- a rare genetic disease of small vessels caused by mutations of the Notch3 gene. This variant is clinically characterized by migraine with aura, stroke and psychiatric symptoms leading to dementia and disability (GUNDA, et al. 2012).
- Mixed dementia - coexistence of similar clinical symptoms of Alzheimer's Disease and Vascular Dementia.

DIAGNOSIS

It is important to point out that the adequate treatment of patients with dementia depends, in the first place, on the correct diagnosis of its etiology and this is one of the greatest challenges worldwide. In addition, when the diagnosis is reached, it occurs at a relatively late stage, which reduces the chances of effective management, since the beneficial effects of current treatments have only been observed in the early stages of the disease. As a result, the World Health Organization has established the diagnosis of dementia as one of its priorities, to ensure adequate treatment, care and support for patients (WHO, 2015). The ability to differentiate the various classifications of Vascular Dementia is substantial to define treatment strategies for each subtype (ALEXANDER, et al. 2022).

The diagnosis of Vascular Disease (VD) is based on criteria that range from clinical history to neuropsychological evaluation and

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neuroimaging tests (computed tomography or magnetic resonance imaging, which is preferred due to the possibility of better identification of lacunar infarctions) (CARAMELLI, 2002).

Within the proposed criteria, the presence of risk factors for VD, such as advanced age, symptomatology, progressive deficit of cognitive function (with emphasis on memory loss) and interference in their activities must raise this diagnostic possibility. Currently, the most accepted criterion for vascular dementia is that of the National Institute of Neurological Disorders and Stroke – Association Internationale pour la reserche et L'enseignement en Neurosciences (NINDS-AIREN), which states that there must be dementia, associated with cerebrovascular disease and a relationship established between both (PARMERA, 2015; CARAMELLI, 2002; GALLUCCI NETO et al 2005).

This relationship can be evidenced with dementia symptoms appearing a few months after a recognized stroke or by a sudden deterioration of cognitive functions or even by cognitive deficits that appear in "levels". Some features reinforce the diagnosis and must be sought in the neurological examination, such as: early presence of gait disorders, report of imbalance, pseudobulbar palsy, early urinary urgency or even changes in personality or mood. The presence of early and progressive amnestic deficit, as well as the absence of vascular lesions on imaging tests or the absence of focal neurological signs make the diagnosis less likely (PARMERA, 2015; RIBEIRA 2004).

TREATMENT AND PREVENTION

Current strategies for the prevention of VD involve the elimination of vascular risk factors and improvement in lifestyle. As additional strategies, they include exercises for maintaining cognitive health and stroke prevention (early diagnosis and prevention of recurrences). Although there are currently no specific treatments for VD, therapeutic regimens are aimed at prevention (statins, antihypertensives, anticoagulants, antiplatelet agents) and symptomatic relief (N-methyl-D-aspartate antagonists, cholinergic agents, oxidative stress-reducing agents) (NGUYEN DH, et al., 2021).

As for drug treatment, currently only two classes of drugs are formally indicated for the treatment of patients with dementia: cholinesterase inhibitors (Donepezil, Rivastigmine and Galantamine) and Memantine, a non-competitive antagonist of the N-methyl-D-aspartate receptor. and dopamine agonist (WELLER J and BUDSON A, 2018; ELAHI FM and MILLER BL, 2017). Current medications approved for AD only improve patients' symptoms without modifying disease progression (SUN BL, et al., 2018).

Given this, treatments with "disease-modifying" drugs that prevent or at least effectively modify the course of dementia are still under investigation (MUNOZ-TORRERO, 2008). These drugs interfere with the pathogenic factors responsible for clinical symptoms, such as the production of extracellular amyloid plaques, intracellular neurofibrillary tangles, inflammation, oxidative damage, cholesterol metabolism, and prevent disease progression (PARIHAR AND HEMNANI, 2004). Currently available medications do not cure, they only ease the symptoms for a brief period. Therefore, it is important to explore new targets and therapeutic agents of natural compounds for the treatment of dementias.

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