

## VASCULAR DEMENTIA REVISED

# VASKULARNA DEMENCIJA: REVIZIJA

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### Summary

Vascular dementia is the second leading cause of dementia, right after Alzheimer's disease. It is a condition with great medical, social and economic burden. Although its concept has been recognized for over a century, disease mechanisms, diagnostic criteria and treatment modalities remain unclear and generate confusion and debate.

Dementia and cerebrovascular disease share risk factors and neuropathology, and may contribute to VaD. Several mechanisms have been proposed, including vascular risk factors (hypertension, diabetes, hyperlipidemia) and behavioral factors (physical inactivity, obesity) as major substrate for both cerebrovascular disease and dementia. Also, macro and micro-embolic events and chronic brain hypoperfusion contribute to vascular dementia.

Having in mind that disease mechanisms for vascular dementia and Alzheimer's disease are overlapping, and that clinical manifestations of cognitive impairment are often very similar, setting the diagnosis of vascular dementia is not an easy task. In clinical research, various diagnostic criteria are proposed. They are based on two major requirements: clinical diagnosis of dementia and its vascular origin.

According to its multicausal nature, vascular dementia stands as a difficult condition to treat. Several therapeutic modalities have been offered; however, further investigation and trials with long-term follow-up are needed.

**Keywords:** Vascular dementia, vascular cognitive impairment, cerebrovascular disease, carotid disease, carotid surgery

### Sažetak

Vaskularna demencija je drugi vodeći uzrok demencije, odmah nakon Alzheimerove bolesti. To je stanje od velikog medicinskog, društvenog i ekonomskog značaja. Iako je njen koncept prepoznat pre više od jednog veka, mehanizmi bolesti, dijagnostički kriterijumi i način lečenja ostaju nejasni, te izazivaju konfuziju i debatu.

Demencija i cerebrovaskularna bolest dele faktore rizika i neuropatologiju, doprinoseći razvoju vaskularne demencije. Vaskularni faktori rizika (hipertenzija, dijabetes, hiperlipidemija) i navike ponašanja (fizička neaktivnost, gojaznost), predstavljaju glavni supstrat za nastanak kako cerebrovaskularne bolesti, tako i demencije. Isto tako, makro i mikro-embolijski događaji u moždanoj cirkulaciji i hronična hipoperfuzija mozga doprinose nastanku vaskularne demencije.

Imajući u vidu da se mehanizmi bolesti vaskularne demencije i Alzheimerove bolesti preklapaju, te da su kliničke manifestacije kognitivnog oštećenja veoma slične, postavljanje prave dijagnoze često nije lak zadatak. U kliničkim istraživanjima su predloženi različiti dijagnostički kriterijumi, zasnovani na dva glavna principa: klinička dijagnoza demencije i njeno vaskularno poreklo.

Zbog svoje multikauzalne prirode, vaskularna demencija predstavlja zahtevno stanje za lečenje. Nekoliko terapijskih modaliteta je ponuđeno, međutim, potrebna su dalja istraživanja i studije sa dugoročnim praćenjem.

**Ključne reči:** vaskularna demencija, vaskularno kognitivno oštećenje, cerebrovaskularna bolest, karotidna bolest, karotidna hirurgija

## INTRODUCTION

Vascular dementia (VaD) is the second leading cause of dementia, right after Alzheimer's disease (AD) (1, 2). In addition, postmortem pathological studies indicate that 15% to 34% of all dementia cases show a significant vascular pathology, either alone or in combination with AD (3).

Although its concept has been recognized for over a century, disease mechanisms, diagnostic criteria and treatment of VaD remain unclear and generate confusion and debate, despite the fact that several clinical criteria have been used for defining VaD (4). Given its growing health, social and economic burden, prevention and treatment of VaD are critical priorities for clinical care and research (5).

In order to illuminate this entity, we reviewed current literature and summarized previous findings related to VaD.

## DEFINING TERMS

The term vascular dementia substantially means "disease with a cognitive impairment resulting from cerebrovascular disease and ischemic or hemorrhagic brain injury" (4). Recently, the term vascular cognitive impairment (VCI) was introduced to comprise the heterogeneous group of cognitive disorders that share a presumed vascular cause and to include both dementia and cognitive impairment without dementia (5). While some authors advocate that VaD and VCI are different terms for the same entity, for the majority VCI represents a much wider field of cognitive dysfunction (Table 1) (4, 6-11).

**Table 1.** Types of vascular cognitive impairment

• Post-apoplectiform dementia
• Vascular dementia
- Cortical multi-infarct dementia
- Subcortical ischemic vascular dementia (SIVD) or Binswanger’s disease
- Single-infarct dementia
- Hypoperfusion dementia
- Dementia caused by specific brain arteriopathy
• Mixed dementia (vascular dementia and Alzheimer’s disease)
• Mild vascular cognitive impairment (does not fulfill criteria for dementia)

Subcortical ischemic vascular dementia (SIVD) or Binswanger’s disease, represents one of the most common forms of VaD, especially in the elderly (12). Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a subtype of SIVD, is a rare disease with the onset occurring between 40 and 50 years of age, and it’s the most frequent hereditary cause of SIVD (13). As symptoms in CADASIL develop several decades before the onset of common degenerative diseases, confounding by concomitant medical conditions is considerably reduced (14). Therefore, CADASIL stands as a model of “pure” vascular dementia (13, 14).

**Disease mechanisms**

Dementia and cerebrovascular disease (CVD) share risk factors and neuropathology, and may contribute to VaD (15). Vascular risk factors (hypertension, diabetes, hyperlipidemia) and behavioral factors (physical inactivity, obesity) are associated with both CVD and dementia (Figure 1) (16, 17). Additionally, observational studies in middle-aged and older adults have found association between VaD and hypertension (18, 19), diabetes (20, 21), hyperlipidemia (22), physical inactivity (23) and obesity (24). Also, insulin resistance, abdominal obesity, dysfunction of the cerebral small-vessel endothelium (i.e. the blood brain barrier) and chronic kidney disease may contribute to or accelerate VaD (25-28).

Vascular risk factors may lead to cerebrovascular dysfunction through pathways mediated by beta-amyloid

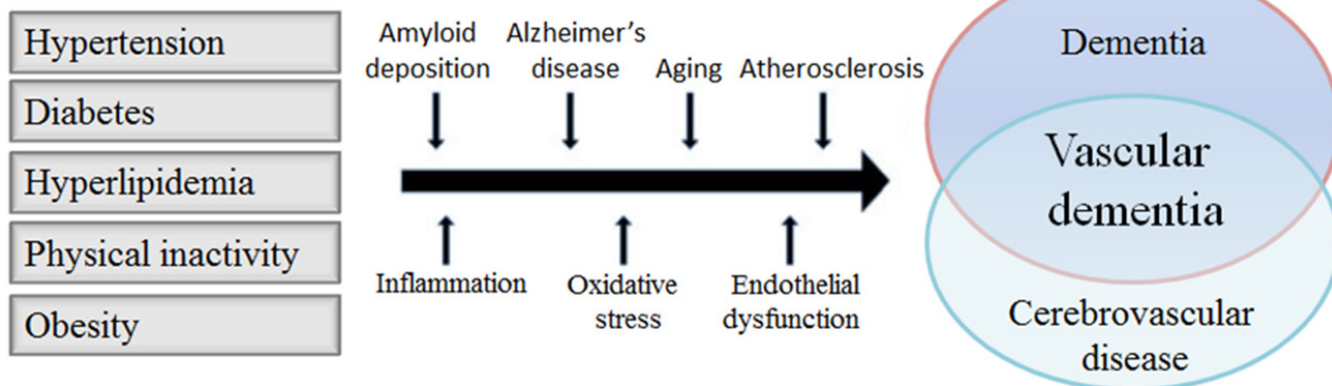
and the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a major source of vascular oxidative stress (29). Several pathogenic mechanisms including AD, amyloid deposition, hypertension, atherosclerosis and aging may converge to cause CVD and VaD through pathways of intravascular oxidative stress and inflammation (25, 29-31).

Moreover, observational studies suggest potential role of inflammation in VaD. In a Japanese case-control study, elevated high sensitivity C-reactive protein and antibodies for Chlamydia pneumoniae were more prevalent in VaD than AD (32). A cross-sectional study found that high interleukin-6 plasma levels were associated with functional impairment in older adults with VaD, but not late-onset AD (33).

Cerebrovascular dysfunction, including blood brain barrier alteration, may compromise cerebral microenvironment and increase the vulnerability of regions critical for cognition (e.g. subcortical white matter, neocortex, hippocampus) to hypoxic-ischemic brain damage, leading to neuronal function failure and cognitive impairment (29). Whether due to shared or additive vascular effects (34), CVD and dementia coexist frequently, particularly in the elderly (35-37).

Atrial fibrillation is known to cause macro-embolic complications, such as stroke, but it may also cause micro-embolic complications, leading to CVD, followed by cognitive impairment (38) or VaD (39). Also, hematologic factors may have an etiological role in VaD. Recent

**Figure 1.** Disease mechanisms of vascular dementia



data may implicate clot formation and micro-infarctions as mechanisms of VaD through hemostatic pathways. High levels of fibrinogen, factor VIII, or plasminogen activation inhibitor 1 have been associated with an increased risk of VCI (40, 41).

Genetic factors may influence the development or course of VCI. Mutations of the *Notch 3* gene on chromosome 19 are leading to CADASIL appearance (42). The apolipoprotein E epsilon 3 polymorphism (43) and the epsilon 4 polymorphism (44), particularly in persons with hypertension or diabetes (45), may be associated with an increased VCI risk, but the data are not conclusive (46, 47). The identification of quantifiable phenotypes that can be reliably and effectively determined in large samples of subjects is the greatest challenge for genetic studies of VaD (48).

Advanced carotid disease and VaD share multiple vascular risk factors (49). The connection between carotid artery stenosis/occlusion and cerebral hemodynamics has been recognized by Spencer and Reid (50). According to the known “Spencer curve”, in mild and moderate carotid stenosis, brain blood perfusion remains stable, until high-grade carotid stenosis occurs (51). Besides cerebral microembolisation, proposed mechanisms of VCI and VaD in patients with advanced carotid disease thus include chronic hypoperfusion (49). A number of previous studies suggested that in asymptomatic individuals, severe carotid disease might be associated with subtle cognitive changes, but the results of those studies have not been consistent (47-56). As the current data on this topic are quite heterogeneous, they need further investigation.

## DIAGNOSTIC CRITERIA

Having in mind that disease mechanisms for VaD, VCI and AD overlap and that clinical manifestations of cognitive impairment are often very similar, setting the diagnosis of VaD is not an easy task. In clinical research, various criteria are proposed for the diagnosis of VaD. They are based on two major requirements: clinical diagnosis of dementia and its vascular origin. The latter requirement is more problematic because of the frequent overlap between cerebrovascular and degenerative disorders, particularly in the elderly. The different set of criteria require various neuroimaging evidence of cerebrovascular disease, focal neurological signs or history of stroke with a temporal relationship with dementia (57).

Four sets of criteria have been essentially used for diagnosing VaD:

- National Institute of Neurological Disorders and Stroke Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria, (58)

- Alzheimer's Disease Diagnostic and Treatment Centers (ADDTTC), (59)
- International Statistical Classification of Diseases, 10th revision (ICD 10), (60) and
- Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV) (61).

NINDS-AIREN, ADDTC and ICD 10 criteria include both clinical and radiological data, while DSM IV criteria require only neuroimaging evidence (58-62).

According to the standard NINDS-AIREN criteria (58), the diagnosis of probable VaD in patients with dementia requires the following conditions: 1) presence of focal neurological signs, such as hemiparesis, lower facial weakness, sensory deficit, hemianopia, dysarthria or Babinski sign; 2) MRI findings of extensive periventricular white matter lesions involving at least 25% of the total white matter or multiple basal ganglia and white matter lacunes and 3) evidence of a temporal relationship between the onset of dementia and stroke or an abrupt deterioration or fluctuating/stepwise course.

Two types of cases were set through visual assessment on MRI: 1) predominantly “white matter cases” characterized by extending periventricular and deep white matter lesions: extending caps or irregular halo (>10 mm broad) and diffuse confluent hyperintensities (>25 mm) and at least 1 lacunar infarct in the deep gray matter; and 2) predominantly “lacunar cases” in which multiple lacunes >5mm in the deep gray matter were associated with at least moderate white matter lesions (57). Additionally, modified NINDS-AIREN criteria for subcortical ischemic vascular dementia require clinical evidence of cerebrovascular disease, i.e. focal signs such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, dysarthria, gait disorders, extrapyramidal signs (other signs such as early urinary symptoms, behavioral symptoms, dysphagia) and brain imaging evidence of cerebrovascular disease (62).

The ADDTC criteria for possible VaD include clinical and neuroimaging evidence of Binswanger disease, but without any specification for this “evidence” (63).

ICD10 criteria for VaD require neuroimaging evidence of cerebrovascular disease “reasonably judged to be etiologically related to dementia” and the presence of focal neurological findings such as unilateral spastic weakness of the limb, unilaterally increased tendon reflexes, extensor plantar response, or pseudobulbar palsy (60).

DSM IV criteria for VaD require only neuroimaging evidence of cerebrovascular disease judged to be etiologically related to cognitive alterations (61).

In CADASIL, brain MRI shows widespread white matter lesions associated with lacunar infarcts of variable

extent or number and developing from the third decade (64). The main clinical manifestations include attacks of migraine with aura, recurrent subcortical stroke, mood disturbances, and a progressive cognitive decline leading to dementia (13).

Beside clinical and brain imaging methods, blood tests also play a role in setting the diagnosis of VaD. Malaguarnera et al. (65) investigated the relationship between plasma homocysteine levels and vitamins involved in its metabolism in AD and VaD. They found that homocysteine levels were significantly increased, whereas folate levels were significantly decreased in patients with VaD. Vitamine B12 showed significantly reduced levels only in AD patients, while vitamin B6 levels were not significantly different between the groups (65).

A most recent study of Chen et al. (66) showed a close correlation between thyroid status and cognitive dysfunction. Serum TT3 and FT3 levels were found to be decreased, whereas serum TSH level was increased, with the decline in cognitive functions. Furthermore, TT3 levels showed a positive correlation, whereas TSH level showed a negative correlation, with the Mini-Mental State Examination (MMSE) scores. The results suggest that thyroid function is associated with cognitive impairments induced by SIVD. Also, thyroid dysfunction could be a risk factor in the development of VaD. Serum TT3 and TSH levels might also be used as biomarkers for VaD.

However, Agarwal et al. (67) have published discrepant results to Chen's study, leaving space for further discussion.

## TREATMENT

According to its multicausal nature, VaD stands as a difficult condition to treat. Referring to a postulate that vascular pathology likely plays a role in initiating cholinergic neuronal abnormalities in VaD, acetylcholinesterase (AChE) inhibitors are presumed to be an effective therapeutic choice (5, 68).

Donepezil use in patients with probable or possible VaD has shown modest treatment benefits in cognition, but not in global functioning as well (69-71). A study of Roman et al showed that hippocampal size is correlated with the effect of donepezil on cognition, which might be a subject in further investigations of donepezil effectiveness in VaD treatment (71). However, safety remains a concern because one trial found a significantly higher risk of death in group of patients treated with donepezil, compared to placebo (1.7% vs 0%) (71, 72). Studies investigating benefits of Galantamine and Rivastigmine use have shown small improvement in cognitive function, but not in a global performance, neuropsychiatric symptoms or activities of daily living (73-76). They

also found greater incidence of gastrointestinal adverse effects (nausea and vomiting) in patients taking Galantamine and Rivastigmine (76, 77). In addition, Rivastigmine use in younger patients showed no benefits and a possible harm (elevated blood pressure, stroke and lethal outcome) (76).

*The N-Methyl-D-aspartate* (NMDA) receptor antagonist Memantine may have neuroprotective properties and improve cognition.<sup>[78]</sup> Two trials have shown modest treatment benefits on cognition, but not global functioning in patients with mild to moderate VaD (79, 80). Memantine, not AChE inhibitors, was associated with lower odds of dropouts and adverse events (72).

Antihypertensive medication is associated with a decreased risk of VaD, with a 5% reduction in VaD risk yearly (81, 82). One cohort study of hypertensive patients with VaD or mixed dementia showed improved or stabilized cognitive scores with control of systolic blood pressure (BP) in the range of 135 to 150 mm Hg; interestingly, systolic BP levels below 135 mm Hg were associated with steeper cognitive declines (83). Several randomized controlled trials and meta-analyses reported various results of antihypertensive treatment on cognitive function (84-97). Although data suggest that well controlled hypertension might be effective in the secondary prevention of VaD, trials with long-term follow-up are needed.

Despite the fact that decreased levels of high-density lipoproteins and elevated levels of total serum cholesterol and low-density lipoproteins are associated with higher risk of VaD, statin role in VaD prevention and treatment remains uncertain (5).

Acetylsalicylic acid may prevent VaD through several mechanisms, including reduced platelet aggregation, decreased circulating  $\beta$ -amyloid production (derived from platelets), vasodilatation and fewer superoxide radicals. However, its use in VaD treatment needs to be determined (5).

Apart from medication therapy, surgical treatment of carotid disease is proposed to be effective method in preventing and treating VaD. Although carotid revascularization shows multiple benefits, its role in cognitive improvement is an ongoing debate (98-101). Most of the studies showed some improvement in cognitive status after carotid endarterectomy or stenting, but not in overall cognitive functioning (100, 101). Further investigation in this field is needed.

## CONCLUSION

Vascular dementia is a significant medical problem, with a great social and economic burden. Despite the



proposed diagnostic criteria and methods, a standard diagnostic set hasn't been established yet. Additionally, none of the current therapeutic methods could stand as a baseline treatment. We are looking forward to the re-

sults of ongoing genetic investigations and future clinical trials, that will hopefully give us answers in mechanisms and treatment of vascular dementia.

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