Major Vascular Neurocognitive Disorder: A Reappraisal to Vascular Dementia

Majör Vasküler Nörokognitif Bozukluk: Vasküler Demansa Yeni Yaklaşım

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Abstract

Major vascular neurocognitive disorder (NCD) is the second leading form of dementia after Alzheimer’s disease, accounting for 17-20% of all dementias. Vascular NCD is a progressive disease caused by reduced cerebral blood flow related to multiple large volume or lacunar infarcts that induce a sudden onset and stepwise decline in cognitive abilities. Despite its prevalence and clinical importance, there is still controversy in the terminology of vascular NCD. Only after the release of Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) (2013) did the American Psychiatric Association define vascular dementia as “major vascular NCD”. This review includes an overview of risk factors, pathophysiology, types, diagnostic and clinical features of major vascular NCD, and current treatment options of vascular NCD regarding to DSM-5 criteria.

Keywords: Vascular dementia, stroke, vascular mild cognitive impairment, major vascular neurocognitive impairment

Öz


Anahtar Kelimeler: Vasküler demans, inme, vasküler ılımlı kognitif bozukluk, majör vasküler nörokognitif bozukluk

Introduction

Vascular dementia (VaD) or vascular major neurocognitive disorder (NCD), is the second leading form of dementia after Alzheimer’s disease (AD), accounting for 17-20% of all dementias (1). Vascular NCD is a progressive disease caused by a decrease in cerebral blood flow related to multiple large volume or lacunar infarcts that induce a sudden onset and stepwise decline in cognitive abilities (1,2). Patients with vascular NCD experience a loss of memory, language, and executive functions such as organizing thoughts and behavior, problem solving, and planning (1). With the release of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the necessity of memory impairment was removed from the criteria for dementia (3).

There was controversy in the history of terminology; in the past few decades, the term multi-infarct dementia (MID) was used...
to define patients who developed dementia after single stroke and multiple strokes, but the term VaD is used regardless of the pathogenesis of lesion. Recently, some authors preferred to use the term vascular cognitive impairment (VCI) as opposed to VaD (3,4). VCI is a syndrome associated with clinical stroke or subclinical cerebrovascular pathologies that cause cognitive deficit in at least one cognitive domain (4). The term VCI covers syndromes from mild cognitive impairment to VaD, which is the most severe form of VCI (4). Diffuse white matter (WM) damage is believed to be the main reason for VCI and VaD (2).

Until the release of DSM-5 in May 2013, the term dementia was used by the American Psychiatric Association (APA) to identify significant declines in cognitive functions causing mental impairment, and a decrease in patient’s life quality (3,5). The term NCD includes a wider spectrum of conditions than dementia (5). DSM-5 uses the term major vascular NCD instead of VaD (3).

### Diagnostic Features of Vascular Neurocognitive Disorder

NCD are a group of disorders, which are subtyped due to etiology and their primary clinical feature is the decline in cognitive abilities (5). The second common subtype of NCD after AD is major vascular NCD. Four major diagnostic criteria were described in DSM-5, and three more criteria were defined to diagnose possible or probable major vascular NCD (5).

As explained in DSM-5, the criteria for NCDs include neurocognitive domains such as complex attention, executive function, learning and memory, language, perceptual-motor, and social cognition (Table 1) (5).

### Risk and Prognostic Factors of Vascular Neurocognitive Disorder

Identification and control of risk factors play a crucial role in the overall management of vascular NCD. Major vascular risk factors and age are strongly related with cognitive decline in vascular NCD (2), and controlling vascular risk factors can prevent, slow, or suspend the progression of decline in cognitive abilities (6). The risk factors of vascular NCD are as follows:

**Age:** Age is the significant risk factor for vascular NCD and other concomitant clinical vascular diseases. Old age increases the risk of vascular NCD and stroke, and the risk of developing dementia after stroke is higher among the elderly (4).

**Hypertension:** Untreated hypertension in middle age can cause vascular NCD in later stages of life or expedite the progression of vascular NCD, as well as inducing hippocampal atrophy and WM damage (1).

**Diabetes:** Diabetes is an important risk factor for cognitive impairment and related mental symptoms; patients with long-term diabetes have an increased risk of developing VCI and vascular NCD (1,4). Glycemic control helps to prevent microvascular, and to a certain extent, macrovascular events, but not stroke (4).

**Metabolic syndrome:** Metabolic syndrome also elevates the risk of progressing from mild cognitive impairment to dementia, but its exact role in VCI and vascular NCD is not clear.

### Inflammation:

Plasma levels of inflammatory proteins, especially \( \alpha-1 \) antichymotrypsin and C-reactive protein, are elevated before the onset of vascular NCD, yielding that these markers of inflammation may also be associated with vascular NCD (4).

**Arterial stiffness:** Arterial stiffness is a well-known and age-related risk factor for vascular NCD related to changes in elastin and collagen levels, and also associated with qualitative changes of arterial walls (4). A negative correlation has been reported between carotid-femoral pulse wave velocity and cognitive abilities (4).

**Depression:** Neuroimaging and pathologic findings reveal a link between late-life depression and several vascular abnormalities (3). Brain WM damage and other subcortical lesions are seen more often in late-life depression (4).

**Lifestyle factors:** Low level of education and lack of social support have been found related with vascular NCD; low physical activity, however, was not related to cognitive decline (4). On the other hand, regular physical activity has a strong relation with higher cognitive abilities and has protective effects on brain health (4).

Body mass index, especially that measured in midlife, has a strong association with dementia; both cachexia and obesity increase the risk of vascular NCD (4).

Folic acid, and vitamins B6 and B12 are present in the metabolism of homocysteine, which is a risk factor for vascular damage (4).

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**Table 1. Diagnostic and Statistical Manual of Mental Disorders-5 diagnostic criteria for major or mild vascular neurocognitive disorder**

| A. The criteria are met for major and mild neurocognitive disorder. |
| B. The clinical features are consistent with a vascular etiology, as suggested by either of the following: |
| - Onset of the cognitive deficits is temporally related to one or more cerebrovascular events. |
| - Evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function. |
| C. There is evidence of the presence of cerebrovascular disease from history, physical examination, and/or neuroimaging considered sufficient to account for the neurocognitive deficits. |
| D. The symptoms are not better explained by another brain disease or systemic disorder. |

**Probable vascular NCD is diagnosed if one of the following criteria exist, if not possible vascular NCD is diagnosed:**

- Clinical criteria supported by neuroimaging evidence for parenchymal injury due to cerebrovascular disease.
- The neurocognitive syndrome is related to cerebrovascular event or events.
- Clinical and genetic evidence exists for cerebrovascular pathology.

**Possible vascular neurocognitive disorder is diagnosed if the clinical criteria are met but neuroimaging is not available and the temporal relationship of neurocognitive syndrome with one or more cerebrovascular events is not established.**

NCD: Neurocognitive disorder
Smoking and heavy alcohol consumption may be risk factors for vascular NCD; smoking, however, has an effect on only some areas of cognitive functioning, probably due to nicotine’s cholinergic activity in brain (4).

**Demographic and genetic factors:** The following risk factors are classified as non-modifiable risk factors for vascular NCD (4):

1. Despite the known relationship between Apolipoprotein E ε4 allele and cardiovascular and AD, recent studies showed no correlation between Apolipoprotein E ε4 allele and vascular NCD (4).
2. Cerebral amyloid angiopathy (CAA), another important risk factor for vascular NCD, is characterized by the formation of amyloid (Aβ) deposits, which change normal vessel walls into fibrillar amyloid within arterioles, venules, and capillaries (5).
3. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which manifests itself with multiple lacunar infarcts, WM lesions, microbleeds, and brain atrophy, is a hereditary condition that increases the risk of vascular NCD (3,5).

**Coronary artery disease:** Coronary artery disease is an independent risk factor for vascular NCD, and studies proved that severity of atherosclerosis in coronary arteries was related with higher risk of vascular NCD (4).

**Stroke:** Cognitive decline that occurs after a stroke is the leading cause of dependency among patients with stroke (6). Although cognitive abilities generally recover after a stroke, some patients show a decline in cognitive functions (7). About 30% of patients who have a stroke develop dementia within three months (6). Stroke characteristics such as lesion volume and location, on the other hand, are less predictive (7). Neuroimaging studies also show an association between post-stroke dementia and pre-existing subcortical WM disease, infarct volume, temporal lobe atrophy, and cortical hypoperfusion (7).

**Chronic kidney disease:** Severe chronic kidney disease is related with metabolic and hypertensive encephalopathy and increased risk of stroke (4).

**Atrial fibrillation:** Atrial fibrillation, mainly not treated with anticoagulation, is a risk factor for stroke and vascular NCD (4).

**Peripheral arterial disease:** Low ankle brachial index and greater carotid-femoral pulse wave velocity were found related with decline in cognitive abilities (4).

**Low cardiac output:** Decreased cardiac output causes systemic and cerebral hypoperfusion, which may have the leading role in the onset and progression of vascular NCD, especially in older patients with systolic heart failure (Figure 1) (4).

**Pathophysiology of Vascular Neurocognitive Disorder**

Cerebrovascular pathologies cause cerebral damage and decline in cognitive abilities. The decrease in cerebral blood flow due to chronic hypoperfusion or thromboembolic events causes hypoxia, oxidative stress, and inflammatory responses (1). The hippocampus, basal ganglia, and WM are very sensitive to hypoperfusion and hypoxia can easily cause lesions that induce cognitive deficits, which are characteristic of vascular NCD (1). Hypoperfusion and hypoxia lead to oxidative stress that induces the imbalance in the ratio of antioxidants and reactive oxygen species, which then triggers vascular endothelial, neuronal and glial damage, mitochondrial dysfunction, and finally neurovascular uncoupling and decrease in cerebral blood flow (1). Oxidative stress also induces vascular inflammation, endothelial dysfunction, and a neuro-inflammatory response (1).

Neuroinflammation develops due to increased permeability and degradation of the blood-brain barrier and infiltration of inflammatory factors (1). These factors cause WM damage and demyelination by oligodendrocyte degeneration (1). Oligodendrocyte damage also causes delays in remyelination, which eventually leads to neural signal delays and cognitive impairment (1).

Microvascular changes are also related with cerebrovascular and degenerative diseases (4). In vascular NCD and AD, microvessels are reduced in number, become curved, and their basement membranes are thickened (4). Due to microhemorrhages, arterioles show “onion skin” type changes and hyaline degeneration (4). Reactive astrocytosis and microglial activation in periventricular WM are thought to be related to expression of hypoxia inducible genes, which indicate local hypoxia (4). CAA is also associated with vascular or perivascular inflammation, which causes vasogenic edema of subcortical WM and a decline in cognitive ability (4).

Despite these studies on pathophysiology of vascular NCD, it is still difficult to determine the exact effect of cerebrovascular pathology on vascular NCD due to its heterogeneous nature (3). Vascular pathologies, for example, may vary in size, number, and location, and are usually seen in older people with or without dementia, and may not be associated with clinical stroke accompanied by AD and other pathologies (4).

Cerebral pathologies in certain locations cause specific defects in cognitive domains (Table 2). Major effects of vascular NCD on cognitive functions can be observed as defects in 4 domains: mood...

![Figure 1. Risk factors, subtypes, and characteristics of major vascular neurocognitive disorder](image-url)

MRI: Magnetic resonance imaging, PET: Positron emission tomography
Table 2. Diagnostic and Statistical Manual of Mental Disorders-5 neurocognitive domains in vascular dementia, clinical features and related anatomical regions

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Definition</th>
<th>Symptoms or observations</th>
<th>Examples of evaluation</th>
<th>Anatomical localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex attention</td>
<td>Sustained attention</td>
<td>Major: Difficulty with multiple stimuli; difficulty holding new information in mind; unable to perform mental calculations; need simplified instructions to perform a task</td>
<td>Sustained attention: Maintenance of attention overtime</td>
<td>Prefrontal cortical, Striatum (caudate, putamen nuclei), Limbic system damage</td>
</tr>
<tr>
<td></td>
<td>Divided attention</td>
<td>Mild: Normal tasks take longer; errors in routine tasks</td>
<td>Selective attention: Maintenance of attention despite stimuli and/or distractors</td>
<td></td>
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<tr>
<td></td>
<td>Selective attention</td>
<td></td>
<td>Divided attention: Attending to two tasks within the same time period</td>
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<tr>
<td></td>
<td>Processing speed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive function</td>
<td>Planning</td>
<td>Major: Difficulty with complex projects; difficulty with multi-tasking</td>
<td>Planning: Ability to find exit to a maze</td>
<td>Dorsofrontal cortical, Prefrontal cortical, Parietal cortical, Cingulate gyrus damage</td>
</tr>
<tr>
<td></td>
<td>Decision making</td>
<td>Mild: Increased effort needed to complete multistage projects</td>
<td>Decision making: Deciding for competing alternatives</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Working memory</td>
<td></td>
<td>Working memory: Holding information for a short period of time to use it</td>
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<td></td>
<td>Responding to feedback</td>
<td></td>
<td>Feedback: Ability to use a feedback for solving problem</td>
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<tr>
<td></td>
<td>Error correction</td>
<td></td>
<td>Overriding habits/inhibition: Ability to choose a more complex solution to be correct</td>
<td></td>
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<tr>
<td></td>
<td>Overwriting habits</td>
<td></td>
<td>Cognitive flexibility: Ability to shift between two concepts, tasks, or response rules</td>
<td></td>
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<tr>
<td></td>
<td>Mental flexibility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Learning and memory</td>
<td>Immediate and recent memory</td>
<td>Major: Repeats self in conversation, cannot keep track of short lists or plans, requires reminders to orient a task</td>
<td>Immediate memory span: Ability to repeat a list of words or digits</td>
<td>Hippocampus, Thalamus, Frontal cortical, Prefrontal cortical, Parietal and parietal cortical damage</td>
</tr>
<tr>
<td></td>
<td>Very-long-term memory</td>
<td>Mild: Difficulty recalling events, and relies increasingly on list making</td>
<td>Recent memory: Assesses the process of encoding new information. Free call, cued call, and recognition memory</td>
<td></td>
</tr>
<tr>
<td>Language</td>
<td>Expressive language</td>
<td>Major: Significant difficulties with expressive or receptive language</td>
<td>Expressive language: Confrontational naming, fluency</td>
<td>Frontal lobe (Broca), Temporal lobe (Wernicke), Thalamus, Arcuate fasciculus damage</td>
</tr>
<tr>
<td></td>
<td>Receptive language</td>
<td>Mild: Noticeable word finding difficulty</td>
<td>Grammar and syntax: omission or incorrect use of prepositions, articles, and auxiliary</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Receptive language: Comprehension performance of actions/activities according to verbal command</td>
<td></td>
</tr>
<tr>
<td>Perceptual-motor</td>
<td>Visual perception</td>
<td>Major: Significant difficulties with previously familiar activities</td>
<td>Visual perception: Line bisection tasks can be used to detect basic visual defect or attentional neglect</td>
<td>Subcortical, Centrum semiovale, Parietal-temporal cortical damage</td>
</tr>
<tr>
<td></td>
<td>Visuo-constructional</td>
<td>Mild: May need to rely more on maps or others’ directions</td>
<td>Visuo-constructional: Hand-eye coordination</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perceptual-motor</td>
<td></td>
<td>Perceptual-motor: Integrating perception with purposeful movement.</td>
<td></td>
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<tr>
<td></td>
<td>Praxis</td>
<td></td>
<td>Praxis: Integrity of learned movements.</td>
<td></td>
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<tr>
<td></td>
<td>Gnosis</td>
<td></td>
<td>Gnosis: Perceptual integrity of awareness and recognition</td>
<td></td>
</tr>
<tr>
<td>Social cognition</td>
<td>Recognition of emotions</td>
<td>Major: Behavior clearly out of acceptable social range</td>
<td>Recognition of emotions: Identification of emotions in images of faces.</td>
<td>Orbitofrontal and prefrontal cortical damage</td>
</tr>
<tr>
<td></td>
<td>Theory of mind</td>
<td>Mild: Subtle changes in behavior or attitude</td>
<td>Theory of mind: Ability to consider other person’s mental state or experience</td>
<td></td>
</tr>
</tbody>
</table>
and social cognition, learning and memory, perceptual-motor, and executive functions (Figure 2).

Types of Vascular Neurocognitive Disorder

A classification is needed because the clinical aspects of vascular NCD can vary based on etiology and type. Vascular NCD can be classified under 8 types;

Small-vessel dementia (subcortical VaD): Subcortical dementia is one of the most common types of vascular NCD caused by ischemia of cerebral WM and multiple lacunar infarcts (8). The term Binswanger’s disease was used to describe the appearance of extensive WM changes on neuroimaging without clinical findings (6). It is now known that WM changes without apparent clinical symptoms occur, especially among the elderly (6). The term leukoaraiosis or thinning of WM should be used to describe the earliest changes in WM usually because of small vessel disease (6). In patients with subcortical VCI, lacunae, extensive WM lesions on neuroimaging and infarcts, demyelination, and gliosis can be observed in pathologic specimens (3).

MID (cortical VaD): MID is used to identify patients who developed dementia after multiple strokes (4). Neuroimaging studies reported multiple cortical infarcts and WM lesions that cause executive dysfunction and memory impairment (3,9).

Hypoperfusion dementia: Hypoperfusion dementia usually involves watershed infarcts and WM lesions in neuroimaging, and pathologically, incomplete WM infarcts (3).

Hemorrhagic dementia: Hemorrhagic dementia is a term used for dementia that occurs after hemorrhagic stroke and hemorrhagic changes can be related to CAA (3). CAA is the most important cause of spontaneous intracerebral hemorrhage and plays an important role in age-related cognitive impairment (4).

Strategic-infarct dementia: Strategic-infarct dementia is defined as cognitive impairment caused by an infarct in a strategic location. Studies reported a relationship between lacunar infarcts involving the thalamus, internal capsule, and basal ganglia, and confusion and memory impairment (7).

Infarcts involving the anterior nucleus of thalamus including mammillothalamic tract, fed mainly by the tuberohyalamic artery, are linked to the mammillary body and hippocampus. The medianodorsal nucleus of thalamus, which is supplied mainly by paramedian artery, on the other hand, is linked to the perirhinal cortex and may lead to a significant decline in executive functioning and amnesia (7,9). Anterior thalamic nucleus and/or mammillothalamic tract lesions are related to selective impairment in memory, but mediiodorsal thalamic nucleus lesions are not (9).

Thalamic and basal ganglia infarctions cause depression in synaptic activity and hypoperfusion in the cerebral cortices. This remote effect of thalamic and basal ganglia infarctions (i.e. diaschisis) on cortical areas is the reason of symptoms such as memory or language dysfunction in strategic infarct dementia (7). Strategic infarcts are often reversible by 12 months, and not a common cause of persistent dementia (7).

Hereditary vascular NCD: The most common hereditary cause of vascular NCD is CADASIL (4). Multiple lacunar infarcts, WM lesions, microbleeds, and brain atrophy can be visualized radiographically in hereditary vascular NCD (3). Patients with CADASIL may experience migraines with aura, mood changes, repeated strokes, and cognitive decline (4). Most CADASIL is caused by Notch3 gene mutations that can be used as a diagnostic marker for sporadic cases (4). Genetic testing is recommended for cysteine-altering mutations in the Notch3 gene in patients with progressive decline in cognitive functions, typical neuroimaging findings, and family history (4).

CAA is characterized by deposition of Aβ in the walls of arterioles and capillaries and it is related with destructive changes in vessel walls such as microaneurysms, loss of smooth muscle cells, concentric splitting, and finally fibrinoid necrosis of arteriolar and capillary walls and perivascular leakage of red blood cells (4).

Mixed dementia: Mixed dementia (or mixed major vascular NCD) is a condition in which abnormalities characteristic of more than one type of dementia occur simultaneously. Physicians may also call mixed dementia “dementia-multifactorial”. AD with major vascular NCD associated with cerebrovascular pathologies is the most common form of mixed dementia (3,7). Infarcts often coexist with AD, and studies showed that infarcts with AD pathology increased the risk of dementia and caused a decline in cognitive functions (4). Mixed dementia is more common than pure AD or vascular NCD among the elderly (7). It is often difficult to detect the main reason of cognitive decline, whether it is vascular factors or underlying AD (4). Both atrophy and vascular pathologies can be observed in mixed dementia, mostly in the medial temporal lobe (3). Potential biomarkers that support concomitant AD are cerebrospinal fluid levels of Aβ and phosphorylated tau, and amyloid imaging.

A diagnosis of major or mild vascular NCD is not made if other disorders including brain tumor, multiple sclerosis, encephalitis, and toxic and metabolic diseases are present with sufficient severity to account for the cognitive impairment.

Figure 2. The major effects of vascular neurocognitive disorder on cognitive functions
Clinical Features of Vascular Neurocognitive Disorder

Patients with major or mild vascular NCD present multiple infarctions with an acute stepwise or fluctuating decline in cognition, and intervening periods of stability and even some improvement. Others may have gradual onset with slow progression, a rapid development of deficits followed by relative stability, or another complex presentation. By contrast, patients with AD deteriorate gradually; many patients with vascular NCD worsen through a series of small steps as strokes occur. For mild vascular NCD, history of a single stroke or extensive WM disease is generally sufficient. For major vascular NCD, two or more strokes, a strategically placed stroke or a combination of WM disease and one or more lacuna is generally necessary.

Clinical evidence of stroke includes documented history of stroke with cognitive decline temporally associated with the event, or physical signs consistent with stroke (e.g., hemiparesis, aphasia, visual field defect, brainstem syndromes). Neuroimaging evidence with MRI or CT comprising one or more large-artery infarcts or hemorrhages, a strategically placed single infarct or hemorrhage (e.g., in the thalamus, basal forebrain, angular gyrus or supramarginalis gyrus), two or more lacunar infarcts outside the brainstem, or extensive and confluent WM lesions.

Apathy, slowed thinking, and deteriorating hygiene are also often noted. Relatively mild stressors may precipitate pathologic laughing or crying. Besides failing memory, patients experience loss of executive functioning, which can show up as the inability to deal with novel tasks. Loss of executive functioning (usually attributed to frontal lobe damage) can be tested directly by asking the patient to identify similarities and differences or to carry out a sequence of steps, as with the Mini-Mental State exam. However, executive functioning is often best evaluated from the history or by observation of some of these behaviors: closely trailing the physician or a companion (imitation behavior); frozen expression until prompted (lack of spontaneity), putting on more than one pair of trousers (perseveration); or repeatedly getting lost on the ward, though oriented at home (environmental dependency). These patients are less likely than patients with Alzheimer’s to have aphasia, apraxia, and agnosia, though any aspect of mental functioning can be affected. Language functions may be manifest as non-fluent or Wernicke aphasia. Vocabulary contracts as phonemic or semantic paraphasia and stereotyped phrases are substituted for real communication. Reading and writing may deteriorate.

The symptoms of vascular NCD depend on the exact location of brain lesion(s), but several characteristics are typical, especially of subcortical ischemic vascular disease. They include early impairment of executive function and attention, slowed motor performance, and slowed processing of information. Episodic memory is less affected than in Alzheimer’s, but personality changes and mood symptoms (depression, lability), abulia and apathy are especially prominent (Figure 2). The development of late-onset depressive symptoms accompanied by psychomotor slowing and executive dysfunction is a common presentation among older adults with progressive small-artery ischemic disease (vascular depression).

Treatment of Vascular Neurocognitive Disorder

There are currently no Food and Drug Administration approved treatment options for major and minor vascular NCD, but in clinical practice, several drugs for the treatment of patients with vascular NCD have been used, but only modest benefits in cognitive abilities were provided (4). Therefore, management of preventable risk factors and symptomatic pharmacotherapy is the main approach in vascular NCD treatment (4). The current treatment strategies in vascular NCD primarily try to control the progression of cognitive dysfunction. The drugs that are most-commonly used in the treatment of vascular NCD are as follows:

**Statins:** Statins are cholesterol-lowering drugs that inhibit HMG-Coa reductase, which is the rate-limiting enzyme for cholesterol synthesis. With oral simvastatin administration in high-fat diet fed rats (5 mg/kg for 4 weeks), anxiety, depression, and decline in cognitive abilities of animals were reversed, and the number of pyramidal neurons were increased (10). Studies also revealed that simvastatin therapy administered 20 mg/kg daily for 2 years contributed to a delay in the progression of WM lesions, only in patients who already had severe WM lesions at baseline (11).

**Memantine:** Memantine, used in the treatment of AD, is an uncompetitive N-methyl-D-aspartate antagonist (1). In clinical studies, memantine treatment (20 mg/day for 28 weeks) improved cognition without decline in global functioning and behavior (12). During the clinical trials for neuroprotective efficacy of memantine, adverse effects such as dizziness and restlessness/agitation at higher doses (40 mg/day) were observed; these effects, however, were mild and dose related (13).

**Donepezil:** Donepezil, a reversible acetylcholinesterase inhibitor, improves cognition and global functioning in patients with vascular NCD by crossing the blood-brain barrier and is well tolerated (1,14). Although donepezil therapy provides cognitive benefits to patients with vascular NCD, its effect on global and functional efficacy is less consistent (4).

**Rivastigmine:** There is some evidence of a benefit with rivastigmine in VCI from three studies. However, this conclusion is based on one large study. The participants in one trial did not have dementia, the other two studies included participants with dementia of different severities. The dose of rivastigmine was different in each study.

**Galantamine:** In clinical trials, galantamine treatment was safe and well tolerated, and effective in improving cognition and executive function in patients with vascular NCD (15). Although some studies showed that galantamine administration could be beneficial for patients with mixed dementia, improvement in daily life activities in galantamine treatment was similar to placebo (4,15).

**Cell-based therapy:** Cell-based therapies such as transplantation of endothelial progenitor cells, bone marrow stromal cells, and human umbilical cord stromal cells (HUCBCs) increase the trophic factor secretion; induce angiogenesis, neurogenesis, and WM remodeling after stroke; and may also reduce cognitive decline (1).

Research revealed that HUCBCs were an effective neurorestorative therapy in rats, and provided vascular and WM remodeling after stroke (16). HUCBC transplantation has the dose-dependent potential to support significant tissue repair and provides cognitive improvement after hypoxic-ischemic brain injury (17).
Mesenchymal stem cell (MSC) treatment is another form of cell-based therapies. MSC transplantation regulates longitudinal changes in cortical thickness and improves cognitive performance in patients with cortical thinning and cognitive decline due to multiple system atrophy, and thus has the potential for use in patients with vascular NCD. Other therapies: Studies on resveratrol, a natural herbal compound, showed that resveratrol reduced hippocampus-dependent cognitive impairment caused by isoflurane anesthesia in aged mice with its anti-inflammatory and anti-apoptotic actions.

Chronic neuroinflammation is related with cognitive loss in vascular NCD and several other neurologic disorders. The tumor necrosis factor-alpha (TNF-\(\alpha\)) synthesis inhibitor, 3,6'-dithiothalidomide, was found to reverse hippocampus-dependent cognitive impairment that occurred due to chronic neuroinflammation (20). According to these results, TNF-\(\alpha\) is a critical mediator of chronic neuroinflammation, and treatment strategies aiming at TNF-\(\alpha\) inhibition could be effective in neurodegenerative diseases (1,20).

Recommendations for Risk Factors

Hypertension: Some studies reported that antihypertensive treatment had a positive effect on reducing the likelihood of developing dementia (4). Young elderly patients benefited more from the treatment than the older population. Stated simply, lowering blood pressure early in life helps prevent the onset of late-life dementia; the positive effects of lowering blood pressure in people aged 80 years and older have not been well documented (4). The duration of treatment also appeared to be associated with the preventive effect of the antihypertensive therapy (4). There are also studies suggesting that some types of antihypertensive therapy are more effective than others; however, there is no firm evidence that there is a stronger relationship between such therapies and dementia (4).

Diabetes: The relationship between treating diabetes/ hyperglycemia and dementia prevention has not been well documented (4).

Lipids: Studies showed that hyperlipidemia treatment helped delay the progression of WM lesions only in patients who already had severe WM lesions at baseline. However, there is not enough evidence to draw firm conclusions about the relationship between hyperlipidemia treatment and dementia prevention.

Other Interventions for Vascular Factors

1. Several studies reported that consuming a Mediterranean-type diet helped prevent cognitive decline (4).
2. Further research is necessary to investigate the relationship between vitamin supplementation and improved cognitive ability (4).
3. Prevention of cognitive impairment may be possible with an active lifestyle and physical activity, but effectiveness of other lifestyle choices is not well established (4,21).
4. Some studies suggested that antiplatelet therapy has beneficial effects on cognitive functions, but the usefulness of antiaggregant therapy for vascular NCD is still not proven (4).

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions


Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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