What are the Main Pathogenetic Features of Vascular Cognitive Impairment?

Kurt A Jellinger*

Institute of Clinical Neurobiology, Vienna, Austria

Abstract
The term vascular cognitive impairment designates a heterogenous group of disorders ranging from mild cognitive impairment to full-blown dementia-vascular dementia-resulting from cerebrovascular lesions involving various brain areas. Current clinical criteria show moderate sensitivity (50-56%) and variable specificity (range 64-98%). The prevalence in autopsy series ranges from 0.03 to 58% (mean 8-15% in Western series, 22-35% in Japan). Major morphological types - multiinfarct and subcortical vascular encephalopathy, strategic infarct dementia, lacunar state, granular atrophy (rare), and ischemic encephalopathy-are caused by atherosclerosis of major cerebral arteries and small vessel disease, resulting from systemic, cardiac and local vascular disease or cerebral amyloid angiopathy. Pathogenesis of vascular dementia is multifactorial, and pathophysiology affects brain areas and neurological networks involved in cognition, memory, behavior, and executive functions. Vascular brain injury in elderly persons often coexists with Alzheimer-type lesions and other pathologies resulting in mixed dementia. The heterogeneity of clinical manifestations, cerebrovascular pathology and their pathogenic factors result in limitations of the accuracy of diagnostic criteria for vascular dementia. Recent standardized and reproducible neuropathological criteria for the assessment of cerebrovascular lesions associated with cognitive impairment need to be validated by prospective clinicopathologic studies.

Keywords
Vascular cognitive impairment, Vascular dementia, Cerebrovascular disease, Small vessel dementia, Neuropathology

Abbreviations
AD: Alzheimer disease; BBB: Blood-brain barrier; CVLs: Cerebrovascular lesions; MCI: Mild cognitive impairment; SID: Strategic infarct dementia; SvaD: Subcortical vascular dementia; SVD: Small vessel disease; VaD: Vascular dementia; VCI: Vascular cognitive impairment; WMH: White matter hyperintensities

Vascular cognitive impairment (VCI) describes a heterogenous group of cognitive disorders ranging from Mild cognitive impairment (MCI) to full-blown dementia-Vascular dementia (VaD)-resulting from Cerebrovascular lesions (CVLs), involving different neuronal networks. They are mainly caused by the following blood vessel diseases: Atherosclerosis (AS) of major cerebral arteries, Small vessel disease (SVD) resulting from systemic, cardiac and local vascular disease, Cerebral amyloid angiopathy (CAA), and cerebral hypoxia. The major patterns of brain lesions distinguish: 1. Multi-infarct encephalopathy, and 2. Subcortical vascular encephalopathy, and 3. Strategic infarct dementia [1-3] (Figure 1 and Figure 2).

Morphological substrates of VaD are related to large and small vessel disease (Table 1).

1. Large vessel dementia: Multi-infarct encephalopathy (about 15% of VCI) featured by multiple large and small infarcts in supply areas or borderzones of major cerebral arteries due to severe AS of extra- and intracra-
Cerebrovascular disease | Cerebrovascular lesions | Dementia type
---|---|---
Atherosclerosis | Ischemic/hemorrhagic infarct | Multi infarct
Small vessel disease | White matter lesions | Strategic infarct
Cerebral amyloid angiopathy | Haemorrhages | Subcortical vascular encephalopathy

Figure 1: Schematic diagram of the three most common cerebrovascular diseases, resulting cerebrovascular lesions and specific types of vascular dementia (modified from [5]).

Figure 2: The major types of cerebrovascular lesions related with cognitive impairment A) Multiple infarct encephalopathy (20-40%); B) Subcortical lesions due to small vessel pathology (40-50%); C) Strategic infarcts (subcortical) (10-15%) (modified from [4]).

Table 1: Subtypes of vascular dementia according to major morphological lesions.

| Condition | Imaging and pathological changes. |
|---|---|
| 1. Multi-infarct dementia (MIE) | Multiple large and/or small infarcts in the supply territories or borderlines of large cerebral arteries, in particular ACM, ACM + ACP, uni- or bilateral. |
| 2. Small vessel dementia (SVD) (subcortical VaD) | Multiple lacunes/microinfarcts in cerebral white matter. Subcortical (leuko-) encephalopathy Binswanger. Diffuse white matter lesions (myelin/axon loss), lacunes enlarged perivascular spaces, residues of microinfarcts or microbleeds. |
| 3. Strategic infarcts dementia | Small or medium-sized infarcts in strategic locations (thalamus, hippocampus, basal forebrain, disruption of subcortico-cortical circuits. |
| 4a. Hypoperfusion dementia | Watershed infarcts or scars in cortical and cortico-subcortical border zones of large cerebral arteries or of cortical and subcortical vessels. Granular cortical atrophy (multifocal cortical microinfarcts or scars-rare). |
| 4b. Hypoxic dementia | Pseudolaminar cortical necrosis mainly in arterial border zones (postischemic lesions). |
| 5. Hereditary (VaD-CADASIL): CARASIL, etc. | Multiple lacunes and white matter lesions. |
| 6. Hemorrhagic dementia | Multiple hemorrhages (subdural, subarachnoidal, intracerebral), multiple cortical and subcortical microbleeds and residues. |
| 7. Venous infarct dementia | Large symmetric congestive hemorrhagic infarcts due to thrombosis of the sagittal sinus or the great vein of Galen. |
| 8. Hippocampal sclerosis | Diffuse or sector CA2 necrosis or gliosis. |
| 9. Alzheimer disease with CVD (mixed dementia) | Combination of AD-type pathology (plaques and tangles) and cerebrovascular changes of different types and locations. |

ACM: Middle cerebral artery; ACP: Posterior cerebral artery; CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.
nial vessels causing local thrombo-embolism, hypoperfusion and cardiogenic emboli, caused by breaking of thrombi from ulcerated lesions in extracranial arteries or heart valves. Inflammatory and rare hereditary angiopathies, e.g. CADASIL, frequently cause smaller infarcts [4].

2. Small vessel disease (SVD)/microangiopathic dementia with microinfarcts, lacunes and microbleeds, predominantly involving subcortical structures (white matter, basal ganglia, intern capsule) due to microvascular changes, e.g., fibrosis, stenosis, hypertensive angiopathy, etc. These changes are present in more than 60% of VCI patients.

   a) Lacunar state with multiple cortico-subcortical lacunes or microinfarcts, found in 32-45% of elderly as the most frequent type of CVLs.

   b) Strategic infarct dementia (SID) with small infarcts in functionally essential brain areas (thalamus, frontocingual cortex, hippocampus) due to SVD or embolism. They destruct neuronal networks that are important for cognition and behavior.

   c) Watershed or borderzone (cortical and/or subcortical) infarcts in cerebral convexities or borderzones between major cerebral arteries or in territories between small deep and superficial vessels.

   d) Subcortical vascular dementia (SVaD) or arteriosclerotic (leuko) encephalopathy type with confluent white matter lesions (demyelination, axonal loss due to lacunar infarcts or related with enlarged perivascular areas), usually sparing subcortical U-fibers [1,5]. White matter hyperintensities (WMH) seen in Magnetic resonance imaging (MRI) in elderly individuals with and without cognitive impairment, are generally associated with SVD and edema. The lesions are caused by disturbances of the Blood-brain barrier (BBB), hypotension and ischemia, but recent studies indicate also relationship to cortical neurodegenerative tau-pathology in Alzheimer disease (AD) [6].

   e) Cerebral microbleeds, associated with increased ischemic stroke risk, are markers of consequences of both hypertensive SVD and CAA [1,2,4].

3. Further pathological substrates of VCI include:

   a) Post-ischemic encephalopathy with:

         • Cortical laminar necrosis mainly in arterial border zones resulting from hypoxia due to cardiac or respiratory arrest;

         • Multiple post-ischemic lesions with cortical/subcortical (micro)infarcts;

         • Hippocampal sclerosis of hypoxic-ischemic etiology, but also associated with neurodegeneration or advanced age.

   b) Hemorrhagic dementia due to primary (hypertensive) intracerebral hemorrhages is rare.

   c) Combined (multifocal) cerebrovascular lesions involving various brain regions, related to different vascular changes.

Clinical Features

Cognitive changes in VCI/VaD are more variable than in AD and are dependent on the particular neuronal substrates related to the vascular pathology, while other functions such as memory, language, executive functions and non-cognitive features, depression and apathy are much more affected; delusions and hallucinations are less frequent [7,8].

Previous diagnostic criteria for VCI/VaD requested the presence of memory loss independent of dementia. Currently, several sets of criteria for the clinical diagnosis of VCI/VaD are used [2,7]: the NINDS-AIREN criteria, the ADDTC criteria, the DSM-V criteria (APA), distinguishing possible, probable and proven VaD (with pathologically proven multiple cerebrovascular lesions/CVLs), the NINDS-CSN criteria, the EFNS guidelines, the consensus statement of the American Stroke Association, and the VASCOG criteria.

Several studies reported moderate sensitivity of clinical criteria (average 50-56%) and variable specificity (range 64-98%) with variable interrater reliability [7,8]. The heterogeneity of clinical manifestations, cerebrovascular pathology and their pathogenic factors result in limitations of the accuracy of diagnostic criteria for VCI/VaD. The limitations of current clinical diagnostic criteria sets for VCI/VaD that poorly reflect the underlying pathology, have been critically discussed recently [2,4,9].

In clinical studies, the prevalence of VaD ranges from 4.5 to 39%, in Western memory clinic- and population-based series 8-15%, in pathological series even 0.03-85.2% with means around 11-15%, and in Japan 23.6-35% [2]. The prevalence studies must be interpreted cautiously since aged subjects with and without dementia show a high frequency of mixed pathologies [5,10].

In elderly patients the prevalence of "pure" VaD morphologically characterized by multiple CVLs without essential concomitant AD-type (Braak neuritic stage < 2.0) and other pathologies ranges from 5 to 78% with mild reduction in the oldest-old, while that of mixed dementia increases with age [1]. Recent studies have emphasized the co-morbidities associated with VaD and AD-like pathology, resulting in mixed dementia. Although there is an established relationship between vascular and degenerative (AD) pathology, the links between the two lesions...
have to be identified. In general, however, vascular brain damage is believed to be an important component of AD pathophysiology [5,10]. However, the impact of cooccurring pathologies on progression of cognitive impairment may depend on the severity of AD pathology [8,10,11].

The pathogenesis of CVLs inducing cognitive impairment is multifactorial, resulting from systemic or local vascular and cardiac disease (Table 2). They affect neuronal networks involved in memory, cognition, behaviour and executive functions (thalamo-cortical, striato-subfrontal, limbic systems). Due to frequent comorbidity in old age, cerebrovascular pathology often coexists with Alzheimer-type lesions and other pathologies. 25 to over 80% of elderly both demented and non-demented individuals show mixed pathologies [4,10]. The systemic interplay of pathogenic factors related to VCI is summarized in (Figure 3).

Standardized neuropathological criteria for the assessment of CVLs associated with cognitive impairment are urgently needed. However, despite several recent suggestions for staging and grading vascular lesions in specific brain areas, due to the high variability of these lesions, no generally accepted and validated criteria are currently available for VCI/VaD [1-4]. A recent collaborative study of nine UK neuropathological centers to formulate evidence-based Vascular Cognitive Impairment Neuropathology Guidelines (VCING) for post-mortem assessment of CVD of relevance for BCI/VaD has shown that various combinations of three pathologies (occipital leptomeningeal CAA, atherosclerosis in occipital white

![Table 2: Pathogenesis of vascular cognitive impairment/vascular dementia.](image)

### Table 2: Pathogenesis of vascular cognitive impairment/vascular dementia.

| Tissue lesions                                    | Multifocal                                                                 | Focal                                                                 |
|---------------------------------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------|
| Systemic disease                                  |                                                                           |                                                                      |
| Atherosclerosis                                   | Multiple lacunes, infarcts, borderline infarcts, cortical granular atrophy, combined cortico-subcortical lesions | Strategic networks (thalamus, caudate, hippocampus, angular, cingulate gyri) |
| Thrombo-embolism                                  |                                                                           |                                                                      |
| Cardiac disease                                   |                                                                           |                                                                      |
| Systemic emboli                                   |                                                                           |                                                                      |
| Hypoperfusion (instable artery pressure)          | White matter lesions (leukoaraiosis, Binswanger)                          | Periventricular white matter lesions                                 |
| Hemorrhagic                                       | Multiple small or large hemorrhages                                       | Focal bleeds                                                         |

![Figure 3: Schematic interplay of pathogenic factors causing vascular cognitive impairment/vascular dementia.](image)

CAA: Cerebral amyloid angiopathy; CBF: Cerebral blood flow (modified from [2]).
matter, and at least one infarct) can be used to report a low, intermediate or high likelihood that CVD contributed to cognitive impairment [12]. Like previous proposals for classification and rating of vascular and related cerebral lesions causing cognitive impairment, the VC-ING needs validation by prospective clinico-pathologic studies. Further clinico-pathological studies and harmonization of neuropathological procedures are needed to validate the diagnostic criteria for VaD in order to elucidate the impact of CVLs and coexistent pathologies on cognitive impairment as a basis for successful preventive and therapeutic options.

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