Part 1 Vascular cognitive impairment

Chapter 1

Introduction: what is vascular cognitive impairment?

José G. Merino and Vladimir Hachinski

Introduction

Vascular cognitive impairment (VCI) refers to a heterogeneous group of conditions in which vascular factors are associated with or cause cognitive deficits. It includes the spectrum of cognitive impairment associated with cerebrovascular disease, subclinical vascular brain injury, or vascular risk factors, and it encompasses all degrees of severity, from very mild to frank dementia [1,2].

Since the early 1960s, our understanding of the role that vascular disease plays in the etiology of cognitive impairment has evolved. Until the 1960s, the most commonly diagnosed etiology of dementia in the elderly was hypoperfusion resulting from atherosclerosis of the neck and brain arteries. In the 1960s and 1970s, however, results of clinical and imaging studies led to the recognition that discrete infarcts could affect cognition. By 1968, C. Miller Fisher was able to state that "cerebrovascular dementia is a matter of strokes large and small" rather than hypoperfusion [3]. In 1974, the concept of multi-infarct dementia (MID) was developed and the Ischemic Score was created to distinguish this from Alzheimer disease (AD), then considered mutually exclusive etiologies of dementia; the score used features such as the presence of vascular risk factors and the manifestations of systemic and cerebrovascular disease [4,5]. In the decade following the description of MID, cerebrovascular lesions other than multiple infarcts were found to negatively impair cognition; this realization led to the wide acceptance of the broader concept of vascular dementia (VaD), and several etiological subtypes were described: MID, strategic infarct dementia, and dementia due to small vessel disease, hypoperfusion, and hemorrhage [6,7]. In the 1990s, several groups of experts developed criteria for VaD that were based on consensus and not on empirical data. By then, as a result of scientific discoveries and societal changes, AD had replaced VaD as the most commonly diagnosed etiology of dementia [8,9].

Since the mid 1990s, the role that vascular factors play in the development of cognitive impairment has been re-evaluated. There has been a shift in emphasis to identify people with milder cognitive impairment, ideally in the presymptomatic (or brain-at-risk) stage, when interventions to alter the course of the disease are possible [10]. The concept of VCI was developed recognizing this heterogeneity in severity and etiology and the fact that vascular disease can initiate, interact with, and potentiate the effects of neurodegenerative processes [11]. Since the start of the twenty-first century, VCI has replaced VaD as the paradigm to understand the association between vascular factors and cognitive decline [11]. The term VCI encompasses a broad range of severity, from very mild cognitive impairment to incapacitating dementia.

The prevalence of VaD is estimated as 3.1% in those older than 75 years and 12% in those older than 85. The prevalence of milder degrees of cognitive impairment associated with vascular causes is even higher [12]. However, because there is a strong interaction and synergism between cerebrovascular and Alzheimer-type pathology, and most elderly patients have some degree of both, vascular disease is probably the most common etiology of cognitive impairment. An etiological classification of VCI includes several subgroups: large extra- and intracranial vascular disease, small vessel disease, hypoperfusion, hemorrhage, and mixed vascular–neurodegenerative pathology. These distinctions, however, are artificial, as some patients have white matter changes, lacunes, cortical infarcts, plaques, and tangles.

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Cerebrovascular disease and cognitive impairment

In community-based series, patients with a history of stroke were four to six times more likely to have dementia than stroke-free individuals [13]. The prevalence of dementia 3 months after a stroke ranged from 6% to 32%, and it was higher in patients with recurrent stroke. The proportion of patients who have cognitive impairment short of dementia 3 months after a stroke is even higher: 25% to 70% [14,15]. In some patients with stroke, the cerebrovascular episode may have exacerbated pre-existing cognitive impairment or dementia, which was often caused by a neurodegenerative process [16,17]. Factors associated with post-stroke cognitive impairment include age, educational level, cognitive status before the stroke, temporal lobe atrophy, white matter changes, cardiac pathology, and the existence of multiple vascular risk factors [16]. While cognitive function may improve in some patients over time, patients with post-stroke cognitive impairment progress to dementia at a rate of 8% per year [18,19].

Population-based studies show that up to 20% of people older than 65 years (and 30% to 50% of patients with vascular risk factors, depression or dementia) have at least one silent infarct, and that the prevalence of these lesions increases with age [20–22]. The term silent infarct implies that they do not lead to symptoms of a stroke, but it is a misnomer because these lesions are associated with subtle neurological abnormalities, frailty, depression, and cognitive impairment. Compared with people without these lesions, people with silent infarcts and normal cognition at baseline have a higher risk of subsequent stroke and twice the risk of developing dementia (including AD) over the next few years [23–26].

Small vessel disease is the cause of 40% to 70% of patients with VaD, and patients with small vessel disease and dementia may constitute a homogeneous subtype of VCI (subcortical ischemic vascular dementia) that is characterized by psychomotor slowness as a result of loss of control of executive cognitive functioning; forgetfulness; changes in speech, affect, and mood; urinary incontinence; and gait disturbance [27]. Imaging studies show subcortical infarcts and white matter changes [28]. Subcortical infarcts increase the risk of dementia substantially [29]. In the Nun Study, for example, nuns whose brains had Alzheimer pathology were 20 times more likely to have dementia if they also had lacunar strokes in the basal ganglia, thalamus, and deep white matter [30].

While lipohyalinosis induced by hypertension is the main cause of lacunar infarcts, other vasculopathies may lead to the brain changes of small vessel disease. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) results from a mutation of *NOTCH3* in chromosome 19q12 that lead to deposition of granular osmophilic material in, and destruction of, vascular smooth muscle cells; progressive wall thickening and fibrosis; and luminal narrowing in small and medium-sized penetrating arteries of the brain, skin, and muscle [31]. The features of CADASIL, an autosomal dominant disorder that can also arise de novo, include migraine headaches, multiple strokes at an early age, changes in the white matter (characteristically involving the temporal poles), seizures, visual abnormalities, and cognitive impairment and dementia. Cerebral amyloid angiopathy (CAA) is an angiopathy in which amyloid accumulates in the vessel wall, leading to lacunar and hemorrhagic (micro- and macro-) strokes and white matter lesions. Occurrence of CAA may lead to cognitive impairment even in the absence of hemorrhage, after controlling for age and AD pathology [32]. Population-based clinico-pathological studies have identified associations between advanced CAA and worse cognitive performance, and these associations remain independent after controlling for severity of AD pathology [33]. Other hereditary vasculopathy syndromes include familial CAA caused by mutations or duplications of the gene for the amyloid precursor protein (APP), autosomal dominant retinal vasculopathy with cerebral leukodystrophy, and cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) [2].

In addition to infarction, cerebrovascular disease leads to other injuries that can be seen on imaging and neuropathological studies and that affect cognition. Some of these lesions, such as white matter changes and cerebral microbleeds (CMBs), are often but not exclusively seen in association with small vessel disease. Cerebrovascular disease causes hypoperfusion, ischemia, and infarction of the white matter and, as a consequence, oligodendrocyte dysfunction, demyelination, and axonal damage [34]. These changes appear on T_2-weighted magnetic resonance imaging (MRI) sequences as a hyperintensity of the white matter, and on computed tomography (CT) they are hypodense. The term leukoaraiosis is used to describe these

lesions; it does not imply a specific etiology [35]. More than 10% of asymptomatic people aged 50–75 years have confluent periventricular lesions, and the prevalence increases with age. Almost 10% of stroke patients, 30–40% of unselected patients from memory clinics, and more than two-thirds of patients in clinical trials of vascular dementia have leukoaraiosis [36]. Patients with AD often have leukoaraiosis, but the changes are more extensive when there is underlying vascular pathology [37]. The risk factors for leukoaraiosis are increasing age, hypertension, diabetes mellitus, hyperhomocysteinemia, atherosclerosis of the large vessels, and a history of smoking. The etiology of the white matter changes seen on MRI may differ by location, as regions of confluent deep white matter changes have myelin loss, gliosis, microinfarcts, and loss of nerve fibers, while periventricular halos have a non-ischemic appearance.

Whereas leukoaraiosis is often found in asymptomatic individuals, even small amounts of white matter abnormalities are associated with significant memory and language impairments in some patients [25,38]. Extensive leukoaraisosis is associated with cognitive impairment, personality change, gait disturbance, motor deficits, urinary incontinence, and an increased risk of death, presumably because these changes interrupt critical neural networks. The severity of leukoaraiosis predicts cognitive decline independently of age, education, and medial temporal atrophy. In a metanalysis of 22 studies, the presence of leukoaraiosis was associated with a threefold increase in the risk of stroke and twice the risk of dementia and of death, as well as a faster rate of decline in global cognitive performance, executive function, and processing speed [39]. The risk of cognitive impairment is greatest for patients with rapid progression of leukoaraiosis [40]. The neuropsychological profile associated with these changes among healthy community-dwelling individuals, stroke patients, and patients with mild cognitive impairment or dementia depends on the extent and location of the white matter changes. Patients with leukoaraiosis of the deep white matter have executive impairment plus slowed processing speed, working memory, and visuospatial abnormalities, with the extent of the lesions determining the severity of the cognitive decline [41–43].

Cerebral microbleeds are small foci of chronic blood products in normal brain tissue detected on T_2*-weighted MRI sequences [44]. These lesions are common in patients with hypertension and CAA. In elderly individuals, CMBs are associated with loss of cognitive functioning. Occurrence of CMBs in the caudate nucleus was independently associated with low global cognitive scores and CMBs in the frontal lobes showed a trend toward lower cognitive scores in patients with CADASIL [45]. In a study of stroke patients, those who had frontal CMBs had lower executive function scores [46].

Cortical and subcortical strokes and changes in the white matter lead to cognitive impairment through diverse mechanisms. Strokes may occur in cortical areas important for language, praxis, and self-awareness. Lesions in the left angular gyrus, inferomesial temporal lobe, hippocampus, anterior and dorsomedial thalamus, left capsular genu, caudate, and right parietal cortex disrupt frontal–subcortical circuits and lead to specific cognitive syndromes (executive dysfunction and impaired recall, behavioral and emotional changes, or abulia and akinetic mutism) [47]. Brain atrophy, long associated with neurodegeneration, also plays a role in the genesis of dementia in patients with cerebrovascular disease, and subcortical strokes may lead to thalamic, cingulate gyrus, and cortical gray matter atrophy [48,49]. Medial temporal atrophy is an important correlate of cognitive dysfunction in stroke patients and may have a stronger association with disease progression than white matter changes [50,51]. Hippocampal volume loss may be related to vascular and neurodegenerative processes. Small vessel disease may lead to loss of neurons in the CA1 region of the hippocampus, similar to that found in patients with AD [52,53].

Mixed pathology

Degenerative AD-type and vascular pathology have a complementary and synergistic relationship in the genesis of cognitive impairment. Population-based neuropathological studies show that the brains of elderly individuals with and without dementia frequently harbor vascular (subcortical white matter lesions, infarcts, microhemorrhages) and neurodegenerative (amyloid plaques, neurofibrillary tangles, Lewy bodies, etc.) changes, and that the presence of both types of pathology impacts the expression of dementia: individuals with mild subclinical AD-type pathology or cerebrovascular disease are more likely to remain free of dementia than those with both types of pathology [11,26,29,30,54–59]. In the Nun Study, for example, for a given load of plaques and tangles, the risk

of dementia was 20-fold higher in nuns who also had lacunar infarcts in the thalamus and basal ganglia [30]. Patients with mesial temporal lobe atrophy, presumably attributable to AD, had an increased risk of dementia after stroke compared with those without atrophy, because hippocampal atrophy may also be caused by vascular disease [60].

In addition, there is experimental evidence to suggest that hypoxia–ischemia may play a role in the pathogenesis of AD (by potentiating amyloidogenesis) and that β-amyloid has potent cerebrovascular effects [61,62]. Both β-amyloid and vascular risk factors lead to oxidative stress, inflammation, and neurovascular unit dysfunction; as a result, the blood–brain barrier is impaired [61]. These changes result in hypoxia, ischemia, hypoperfusion, demyelination, and impaired repair of white matter; these appear as leukoaraiosis on CT and MRI and contribute to cognitive impairment. Ischemia-induced endothelial changes increase the cleavage of amyloid precursor protein, promote tau phosphorylation, inhibit clearance of β-amyloid, and may lead to the development of plaques [61,62]. Genes implicated in the development of vascular risk factors and stroke, and the intermediate phenotypes, and genes that affect tissue response to ischemia (ischemic tolerance, neuroplasticity, etc.) are important in the development of VCI. In addition, there is an interaction with genes involved in AD [63].

Recent large epidemiological studies demonstrate that AD and cerebrovascular disease have risk factors in common [59,64]. Hypertension in midlife may induce small vessel disease and stroke, impair vascular regulatory mechanisms, promote cerebral hypoperfusion, and increase the risk of dementia, particularly AD [65]. Adult-onset diabetes mellitus increases the risk of cognitive impairment, VaD, and AD [66,67]. Insulin resistance has also been associated with AD, as has the metabolic syndrome [68,69]. The association of hyperlipidemia and dementia is less robust, but atherosclerosis of the carotid and the coronary vessels has been associated with dementia [62,70,71]. The presence of several vascular risk factors in middle age may increase the risk of late-life dementia 16-fold [72]. As discussed above, these risk factors promote amyloidogenesis in addition to cerebrovascular changes in the brain. Despite the findings from epidemiological and experimental studies, however, a US National Institutes of Health State-of-the-Science Conference found that the evidence to support the association of a modifiable risk factor with reduced risk of AD was weak, and that much work is needed in this area. [73,74].

Clinical features and diagnosis

Because VCI is a heterogeneous condition, there is no "typical" patient with VCI. The severity of cognitive impairment ranges from prodromal very mild to severely disabling, and the clinical features may be characterized by executive dysfunction or a classical AD phenotype. The presentation of VCI depends on the location and extent of the cerebrovascular disease and the severity of any coexisting neurodegenerative pathology. Patients with multiple cortical strokes may have hemiparesis, sensory loss, corticospinal signs, and visual field defects, whereas those with predominately subcortical disease and leukoaraiosis may have gait disturbance, urinary incontinence, and pseudobulbar features [38,75]. Patients with CADASIL have migraine headaches, multiple strokes, white matter lesions, seizures, vision problems, and personality changes.

The severity of VCI ranges from mild cognitive impairment–no dementia to severe vascular or mixed dementia, and there is no pathognomonic pattern of cognitive deficits. Executive dysfunction is the earliest and most common manifestation of cerebrovascular disease. Single strategic infarcts may lead to a discrete location-specific cognitive syndrome, while subcortical lesions may affect a variety of cognitive domains, with a predominance of executive dysfunction: slowed motor, cognitive, and information-processing speed; impairments in task shifting; and deficits in working memory [18,37,42]. Memory loss predominates in patients with mixed pathology, particularly later in the course of the disease, when the cognitive profile is similar to that of AD. Neuropsychological protocols used to evaluate patients with suspected VCI must be sensitive to a wide range of abilities yet focus on the assessment of executive function.

There are no pathognomonic radiological features of VCI. Neuroimaging studies in patients with VCI are not diagnostic but descriptive; they provide information about the extent of cerebrovascular disease, changes in the white matter, brain atrophy, and presence of other pathologies. Some imaging features are suggestive of specific conditions associated with VCI. Patients with hypertension and CAA have leukoaraiosis, subcortical infarcts, and CMBs. The CMBs in

patients with CAA are frequently found in the gray–white matter junction, particularly in the back of the brain, while in patients with hypertension they tend to be in the deep nuclei, basal ganglia, and brainstem. The white matter changes in patients with CADASIL involve the temporal lobe.

There are no formal diagnostic criteria for VCI. Current criteria for VaD identify patients in the later stages of the disease – the dementia phase – and, paradoxically, because they are meant to exclude patients with neurodegenerative dementia, are based on the AD paradigm, with memory loss as the most prominent clinical feature. They also require imaging evidence of cerebrovascular disease, but because of the requirement for a temporal relationship of the onset of dementia with an infarct, they only identify patients with post-stroke dementia [76,77]. Furthermore, these criteria do not identify the same patients [76,78,79]. Criteria for subcortical vascular dementia in clinical trials have been developed [27]. In order to develop evidence-based criteria and address these shortcomings, the National Institute of Neurological Disorders and Stroke and the Canadian Stroke Network convened a group of experts in 2006 to develop harmonization criteria and define the clinical, neuropsychological, neuroimaging, and neuropathological data that should be collected in an unbiased way and, when integrated in a systematic fashion, will be the basis for the development of diagnostic criteria [80].

Recently, a writing group of the American Heart Association/American Stroke Association proposed a practical approach to the classification VCI [2]. These criteria do not require the presence of memory abnormality and consider dementia and mild cognitive impairment. The criteria differentiate dementia from mild cognitive impairment based on the number of cognitive domains affected and their severity. Vascular dementia is considered to be present when there is a decline in cognitive function from a prior baseline and a deficit in performance on two or more cognitive domains that are of sufficient severity to affect activities of daily living; four domains should be tested: executive/attention, memory, language, and visuospatial function. The presence of VaMCI is diagnosed when activities of daily living are minimally impaired and one or more cognitive domain is affected; it is classified according to the affected domain: amnestic, amnestic plus other domains, non-amnestic single domain, or non-amnestic multiple domains. The VaD or VaMCI is classified as probable when there is a clear temporal relationship between a vascular event and the cognitive decline or a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology. If the relationship between cerebrovascular disease and cognitive decline is not clear, the certainty of the diagnosis is diminished, or the vascular syndrome is associated with another disease process associated with cognitive impairment, the qualifier of possible is used [2].

Conclusions

Vascular cognitive impairment refers to any impairment associated with or caused by vascular factors. Its importance lies in that the vascular component is treatable and its consequences preventable. Although vascular etiologies are varied, the commonest types of cerebrovascular disease are the so-called "silent strokes" that occur six times more often than clinical strokes. Their presence has been underestimated clinically and epidemiologically since the most common screening instrument used both in clinical and epidemiological studies is the Mini Mental State Examination. This tool is sensitive to memory impairment but not to executive function changes, the hallmark of VCI. It is likely that simple screening instruments, such as recommended by the VCI Harmonization Standards, would lead to the identification of a larger number of individuals with VCI who can then be treated. We have enough evidence to treat vascular risk factors on the expectation that it will not only diminish the likelihood of stroke and VCI, but perhaps delay onset of AD.

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Part 1 Vascular cognitive impairment

Chapter 2

Vascular cognitive impairment in the memory clinic

Paige Moorhouse and Kenneth Rockwood

Introduction

When assessing cognition, four clinical questions emerge that help guide the practitioner [1]:

1. Does this patient with a cognitive complaint have a cognitive problem?
2. Is the cognitive problem caused by dementia or by something else?
3. If dementia is present, what is the cause?
4. What is to be done?

In reviewing the clinical presentation of vascular cognitive impairment (VCI) we will focus on the last three.

Vascular cognitive impairment is a heterogeneous group of cognitive disorders that share a vascular cause. Although the semantic construct of VCI is fraught with challenges, the problem it describes remains clinically important because of its prevalence, cost, and opportunities for prevention. This chapter focuses on the clinical subtypes of VCI while providing insight into the history of the construct, its neuropathological and neuroradiological correlates, as well as current developments for treatment and prevention.

The history of the terminology

While it is currently largely agreed that VCI is a clinical diagnosis, and that neuropathology and neuroradiology remain supportive (but not diagnostic) tools [2], a brief review of the history of the terminology sheds light on how the understanding of the syndrome has evolved. In fact, the terminology offers a kind of carbon dating test for neurologists, providing immediate and useful information about their training cohort and camp.

For generations, "senile dementia" was the term applied to describe dementia believed chiefly to be caused by "hardening of the arteries" [3]. Later, the term multi-infarct dementia was adopted to describe dementia resulting from multiple cortical or subcortical infarcts (which may occur in sequence or simultaneously) [4]. It was thought to account for up to 15% of dementias [5]. The term multi-infarct dementia was variably used interchangeably with vascular dementia (VaD), the latter being a broader construct that improved upon multi-infarct dementia by allowing more flexibility in the size and distribution of neuroimaging abnormalities (from single strategic infarcts to leukoaraiosis) that could be considered supportive of the diagnosis [6,7].

The VaD construct has since been superceded by VCI for two main reasons. First, VCI allows for inclusion of increasingly recognized dementias with mixed neurodegenerative (most commonly Alzheimer disease (AD)) and vascular features [8] and acknowledges that these features can act synergistically [9,10] (a concept that while pivotally important in advancing our understanding of the syndrome, may prove to be the construct's undoing). Second, VCI represents an important step away from the "Alzheimerization of dementia" (operationalized by multiple sets of diagnostic criteria (Table 2.1) [6,7,11,12] because it allows inclusion of clinical presentations in which memory impairment is not one of the cognitive domains affected, and clinical presentations of cognitive impairment from a presumed vascular cause that was not severe enough to meet the criteria for dementia (vascular cognitive impairment, no dementia (VCIND)).

Vascular cognitive impairment is, therefore, global diagnostic category that includes VaD (including post-stroke and multi-infarct dementia), cognitive

The Behavioral and Cognitive Neurology of Stroke, ed. Olivier Godefroy. Published by Cambridge University Press.

Table 2.1. Five sets of diagnostic criteria for cognitive impairment in association with vascular disease

Diagnostic criteria	Construct	Features	Criticism
DSM-IV [11]	Vascular dementia	Focal neurological signs and symptoms or laboratory evidence of focal neurological damage judged to be related to the clinical presentation	Requires memory impairment as one of the cognitive domains affected Definitions lack detail Does not include VCIND
DSM-V	Vascular cognitive disorder	The establishment of the presence of a cognitive disorder *and* the determination that vascular disease is the dominant, if not only, pathology that accounts for the cognitive deficits *Mild*: decline in one cognitive domain with function essentially intact *Major*: decline in two or more cognitive domains with impact upon function	Less emphasis on mixed (AD/VaD) type dementia
ADDTC [6]	Ischemic vascular dementia	Evidence of two or more strokes by history, neurological signs, or neuroimaging (with at least one infarct outside the cerebellum) Or, in the case of a single stroke, a clear demonstration of a temporal relationship between the stroke and cognitive presentation	
ICD-10 [12]	Vascular dementia	Four subtypes: vascular dementia of acute onset, multi-infarct dementia, subcortical vascular dementia, mixed or unspecified dementia	Difficult to apply clinically, too selective
NINDS-AIREN [7]	Vascular dementia	Cognitive decline in memory *and* two other cognitive domains severe enough to interfere with activities of daily living *and* clinical and radiographic evidence of cerebrovascular disease *and* a relationship between neuroimaging and clinical presentation (onset of dementia within 3 months following a stroke or abrupt onset of cognitive impairment or fluctuating stepwise progression of cognitive decline)	Requirement for cognitive domains affected is less permissive compared with ADDTC criteria Requirement for neuroimaging evidence of cerebrovascular disease is more strict Does not include VCIND Temporal relationship with cerebrovascular event is strict

AD, Alzheimer disease; ADDTC, Alzheimer Disease Diagnostic and Treatment Centers; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; ICD-10, *International Statistical Classification of Diseases and Related Health Problems*, 10th revision; NINDS-AIREN, National Institute of Neurological Disorders and Stroke and the Association Internationale Pour la Recherche et "Enseignement en Neurosciences;" VaD, vascular dementia; VCIND, vascular cognitive impairment, no dementia.

impairment of mixed (AD and VaD) origin, and VCIND. The distinction between VCIND and mild cognitive impairment [13] is worth noting as the two should not be used interchangeably. Non-amnestic mild cognitive impairment is likely to be at least partly vascular in origin but other subtypes of mild cognitive impairment also show progression to VCI [14,15].

In the upcoming *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, the VCI construct seems likely to be replaced by "Vascular Cognitive Disorder" (VCD), which is further subdivided into mild VCD (to replace VCIND) and major VCD to encompass those forms of cognitive impairment with a vascular cause that meet the criteria for dementia. The VCD category is proposed to improve upon the VaD construct by expanding to include cognitive impairment that does not meet the criteria for dementia, as VCI of course did, and, as was also the case for VCI, remove the emphasis on memory as one of the cognitive domains that should be affected to make the diagnosis. The proposed criteria for VCD will require the establishment of the presence of a cognitive disorder; and the determination that vascular disease is the dominant if not exclusive pathology that accounts for the cognitive deficits [16].

Ever-changing terminology and the ongoing debate regarding the precision of the construct [17,5] have posed significant challenges to ongoing research in the area. Estimates of incidence and prevalence of VCI rely on varied definitions. Similarly, the external validity of research studies and completion of metanalyses are hampered by the varying diagnostic criteria used. Incomplete agreement on terminology has also undermined development of standardized language and criteria for vascular lesions in neuropathology and neuroimaging [18].