SECTION 1

Diagnosis

1

Diagnosing vascular cognitive impairment and dementia: concepts and controversies

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Introduction

Vascular cognitive impairment, the recent modification of the terminology related to vascular burden of the brain, reflects the all-encompassing effects of vascular disease or lesions on cognition. It incorporates the complex interactions between vascular etiologies, risk factors and cellular changes within the brain and cognition. The concept covers the frequent post-stroke cognitive impairment and dementia, as well as cerebrovascular disease (CVD) as the second most common factor related to dementia.

Post-stroke cognitive impairment and dementia are more frequent than traditionally recognized (Pohjasvaara *et al.*, 1997). Further CVD is the second most common cause of dementia (Lobo *et al.*, 2000; Rockwood *et al.*, 2000). CVD as well as vascular risk factors including arterial hypertension, history of high cholesterol, diabetes, and forms of heart disease are independently associated with increased risk of cognitive impairment and dementia (Kivpelto *et al.*, 2006). In addition to these vascular factors, CVD, infarcts and white matter lesions may trigger and modify progression of Alzheimer's disease (AD) as the most common cause of neurodegenerative dementia (Roman *et al.*, 2006; Snowdon *et al.*, 1997). Whilst CVD is preventable and treatable it clearly is a major factor in the prevalence of cognitive impairment in the elderly world-wide (Hachinski, 1992; O'Brien *et al.*, 2003).

Concepts on vascular burden of the brain

During the 1980s and the early 1990s, almost all cerebrovascular injury leading to dementia was ascribed to large cortical and subcortical infarcts, so called multi-infarct dementia (MID) (Erkinjuntti and Hachinski, 1993). The concept of vascular dementia (VaD) was introduced to further refine the description of dementias caused by infarcts of varying sizes, including the smaller lacunar and microinfarcts (Roman *et al.*, 1993). VaD appropriately defined a group of heterogeneous syndromes of vascular origin of which subcortical vascular disease was considered an important subtype (Roman *et al.*, 2002). Although this was an important step forward, it was not adequate to describe the vascular causes of early cognitive impairments, which might lead to a spectrum of dementing illnesses. In addition, the impact of CVD and vascular risk in AD has prompted reconsideration of the broad implications of vascular disease on cognitive function (de la Torre, 2004; DeCarli, 2004; Skoog *et al.*, 1999).

Vascular cognitive impairment (VCI) is currently considered the most recent modification of the

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terminology to reflect the all-encompassing effects of vascular disease or lesions on cognition and incorporates the complex interactions between vascular etiologies, risk factors and cellular changes within the brain and cognition (Roman *et al.*, 2004; O'Brien *et al.*, 2003).

Vascular cognitive concept

The recognition of AD as the commonest cause of dementia led to the development of operational criteria for the diagnosis of dementia in general. The criteria included early and prominent memory loss, progressive cognitive impairment, evidence of irreversibility, and presence of cognitive impairment sufficient to affect normal activities of daily living (ADL). Other definitions of dementia required variable combinations of impairment in different domains of cognition, including executive dysfunction (Erkinjutti *et al.*, 1997). These definitions could, however, result in markedly different prevalence estimates and, therefore consequences for health care planning.

The characteristic episodic memory impairment apparent in AD is attributed to atrophy of the medial temporal lobe. In contrast, cerebrovascular lesions do not necessarily have the same regional predilection. The emphasis of the current dementia criteria limited to episodic memory underestimates the vascular burden on cognition as well as potentially losing sight of effective prevention and treatment strategies. Accordingly, it has been suggested that the "Alzheimerized" dementia concept should be abandoned in the setting of CVD, and indeed this was one of the motives behind the development of the broader category of VCI (Bowler *et al.*, 1999; O'Brien *et al.*, 2003).

VCI refers to all etiologies of CVD including vascular risks which can result in brain damage leading to cognitive impairment. The impairment encompasses all levels of cognitive decline, from the earliest deficits to a severe and broad dementia-like cognitive syndrome (Bowler *et al.*, 1999; O'Brien *et al.*, 2003). VCI cases that do not meet the criteria for dementia can also be labeled as VCI with no dementia or vascular cognitive impairment no dementia (vascular CIND) (Rockwood *et al.*, 2000). These patients have also been labeled as vascular mild cognitive impairment similar to that of amnestic mild cognitive impairment (MCI) for AD (Petersen *et al.*, 2002).

VCI may include cases with cognitive impairment related to hypertension, diabetes or atherosclerosis, transient ischemic attacks, multiple cortico-subcortical infarcts, silent infarcts, strategic infarcts, small vessel disease with white matter lesions (WMLs) and lacunae, as well as AD pathology with co-existing CVD (Kalaria *et al.*, 2004). VCI can also encompass those patients who survive intracerebral and other intracranial hemorrhages but are left with residual cognitive impairment. The concept and definition of VCI or vascular CIND are still evolving (Roman *et al.*, 2004), but it seems clear that the diagnosis should not be confined to a single etiology comparable to the traditional "pure AD" concept. The two main factors to be defined in VCI are the severity of cognitive impairment, and the pattern of affected cognitive domains (O'Brien *et al.*, 2003).

Vascular burden of the brain: size of the problem

Estimates of the population distribution of VCI and its outcomes is influenced by the variety of definitions used (Lobo *et al.*, 2000). For example, if AD with CVD or the previously defined VaD with AD pathology is included, then VCI would most certainly be the most common cause of chronic progressive cognitive impairment in elderly people (Rockwood *et al.*, 2000). In a Canadian study, the prevalence of VCI has been estimated at 5% in people over age 65–90 years. These included patients with CIND. The prevalence of vascular CIND, however, was 2.4%; that of AD with CVD was 0.9%, and of VaD alone was 1.5%. By comparison, the prevalence of AD without a vascular component, at all ages up to age 85 years, was 5.1%, and was determined to be less common than VCI (Rockwood *et al.*, 2000). The Canadian

studies also emphasize that failure to consider VCI without dementia (i.e. vascular CIND) underestimates the prevalence of impairment and risk for adverse outcomes associated with VCI.

Post-stroke cognitive impairment

Post-stroke cognitive impairment is frequent, although it has been a neglected consequence of stroke. An example of a detailed clinical study is the Helsinki Stroke Ageing study (Pohjasvaara *et al.*, 1997). Cognitive impairment 3 months after ischemic stroke was present in one domain in 62% and in two domains in 35% of the patients aged 55–85 years. The cognitive domains affected included short-term memory (31%), long-term memory (23%), constructive and visuospatial functions (37%), executive functions (25%), and aphasia (14%) (Pohjasvaara *et al.*, 1997).

Post-stroke dementia

The frequency of post-stroke dementia varies from 12 to 32% within 3 months to 1 year after stroke (Leys *et al.*, 2005). In the Helsinki study, the frequency was 25% 3 months after incident stroke, and the frequency increased with increasing age: 19% among those aged 55–64 years, and 32% in those aged 75–85 years (Pohjasvaara *et al.*, 1997). The incidence of post-stroke dementia increases with a longer follow-up time from 10 at 1 year to 32% after 5 years (Leys *et al.*, 2005). A history of stroke increases the risk of subsequent dementia by a factor of 5 (Leys *et al.*, 2005; Linden *et al.*, 2004).

Determinants of post-stroke dementia include, among others, high age, low education, pre-stroke dependency and cognitive impairment (Leys *et al.*, 2005). Risk factors of incident post-stroke dementia include epileptic seizures, sepsis, cardiac arrhythmias and congestive heart failure (Leys *et al.*, 2005; Moroney *et al.*, 1996). In one large cohort study, the independent clinical correlates of post-stroke dementia included dysphasia, major dominant stroke syndrome, history of prior CVD and low education (Pohjasvaara *et al.*, 1998). Brain lesion correlates of post-stroke dementia include a combination of infarct features (volume, site), the presence of white matter lesions (extent, location), as well as brain atrophy (Leys *et al.*, 2005; Pohjasvaara *et al.*, 2000). Important critical locations include dominant hemisphere and lesions affecting the prefrontal–subcortical circuit. Lesions mediating executive dysfunction are critical (Vataja *et al.*, 2003). Concomitant behavioral problems and depression relate to dependency (Vataja *et al.*, 2005).

Vascular dementia

Vascular dementia, defined as the subset of VCI patients who fulfill the traditional Alzheimer-type dementia criteria, is considered the second most common cause of dementia accounting for 10–50% of the cases, but this depends on the geographic location, patient population, and use of clinical methods (Lobo *et al.*, 2000). The prevalence of VaD had been reported to range from 1.2 to 4.2% in persons aged 65 years and older (Helsert and Brayne, 1995). Using population-based identification of persons aged 65 years and above, the European collaborative study reported that the age-standardized prevalence of dementia was 6.4% (all causes), 4.4% for AD and 1.6% for VaD (Lobo *et al.*, 2000). In this study, 15.8% of all the cases had VaD and 53.7% AD (Lobo *et al.*, 2000). However, these studies have not estimated the size of the AD with CVD population in more detail. The incidence of VaD increases with increasing age, without any substantial difference between men and women (Fratiglioni *et al.*, 2000). The reported incidence estimates of VaD vary between 6 and 12 cases per year in 1000 persons aged 70 years and older (Hebert and Brayne, 1995).

Risk factors of cognitive impairment and dementia

It is now apparent that the traditional vascular risk factors and stroke are also independent factors for the clinical presentation of mild cognitive impairment and AD (Skoog *et al.*, 1999). The important

independent mid-life risk factors of clinical AD include arterial hypertension, high cholesterol, diabetes, obesity, and reduced physical activity, among others (Kivpelto *et al.*, 2006; Skoog *et al.*, 1999).

Risk factors associated with VCI include risks for CVD, stroke, infarcts and ischemic white matter lesions. Besides completed clinically symptomatic infarcts, also called silent infarcts, the presence of white matter lesions also relates to higher dementia risk (Prins *et al.*, 2004; Vermeer *et al.*, 2003). Similarly to AD, the risks for VCI may be considered under demographic (e.g. age, education), vascular (e.g. arterial hypertension, atrial fibrillation, myocardial infarction, coronary heart disease, diabetes, generalized atherosclerosis, lipid abnormalities, smoking), genetic (e.g. family history and specific genetic features), and ischemic lesion-related (e.g. type of CVD, site and size of stroke) variables (Gorelick, 1997; Skoog, 1998). Hypoxic ischemic events (cardiac arrhythmias, congestive heart failure, myocardial infarction, seizures, pneumonia) giving rise to global cerebrovascular insufficiency are important risk factors for incident dementia in patients with stroke (Moroney *et al.*, 1997). Increasing evidence also suggests that reducing the burden of vascular risk decreases the prevalence of dementia (DeCarli, 2004; O'Brien *et al.*, 2003; Skoog *et al.*, 1999).

Subtypes of vascular dementias

VaD, as well as VCI, encompasses many clinical features which themselves reflect a variety of vascular mechanisms and changes in the brain, with different causes and neurological outcomes. The pathophysiology is attributed to interactions between vascular etiologies (CVD and vascular risk factors), changes in the brain (infarcts, WMLs, atrophy), and host factors (age, education) (Chiu, 1989, 1998; Desmond, 1996; Erkirjuntti and Hachinski, 1993; Roman *et al.*, 1993; Tatemichi, 1990).

The main subtypes of previously defined VaD included in current classifications are cortical VaD or MID, also referred to as post-stroke VaD, subcortical ischemic vascular disease and dementia, (SIVD) or small vessel dementia, and strategic infarct dementia. Hypoperfusion dementia resulting from global cerebrovascular insufficiency is also included. Further subtypes include hemorrhagic dementia, hereditary vascular dementia (e.g. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)), and AD with CVD.

Cortical VaD or multi-infarct dementia

Cortical VaD (MID, post-stroke VaD) has been traditionally characterized by a relatively abrupt onset (days to weeks), a step-wise deterioration (some recovery after worsening), and a fluctuating course (e.g. difference between days) of cognitive functions (Chui *et al.*, 1992; Erkinjuntti, 1987; Erkinjuntti and Machinski, 1993; Roman *et al.*, 1993). Cortical VaD relates predominantly to large vessel disease and cardiac embolic events. It is a syndrome, not a disease entity, related to strokes, and rarely fulfills current criteria modeled on Alzheimer-type dementia. It is characterized by predominantly cortical and cortico-subcortical arterial territorial and distal field (watershed) infarcts. The early cognitive syndrome of cortical VaD includes some memory impairment, which may be mild, and some heteromodal cortical symptom(s) such as aphasia, apraxia, agnosia and visuospatial or constructional difficulty. In addition, most patients have some degree of dysexecutive syndrome (Mahler and Cummings, 1991). Due to the multiple cortico-subcortical infarcts, patients with cortical VaD often have additional neurological symptoms, such as visual field deficits, lower facial weakness, lateralized sensorimotor changes and gait impairment (Erkinjuntti, 1987).

Subcortical VaD

Subcortical ischemic vascular disease and dementia (SIVD) or small vessel dementia incorporates two entities: "the lacunar state" and "Binswanger's disease" (Roman *et al.*, 2002). Whether the SIVD syndrome can be considered as a distinct disease is

debatable. However, as a syndrome it may be readily confused with AD in view of the neuronal loss and co-existing vascular factors. The onset is variable, as reported by Babikian and Ropper (1987): 60% of the patients had a slow onset, and only 30% an acute onset of cognitive symptoms. The course was gradual without (40%) and with (40%) acute deficits, and fluctuating in only 20% (Babikian and Ropper, 1987). There is often a clinical history of "prolonged (transient ischemic attack) TIA" or "multiple TIAs", which are mostly small strokes without residual symptoms and with only mild focal findings (e.g. drift, reflex asymmetry, gait disturbance).

SIVD is attributed to small vessel disease and is characterized by lacunar infarcts, focal and diffuse ischemic WMLs, and incomplete ischemic injury (Erkinjuntti, 1987; Roman *et al.*, 2002; Wallin *et al.*, 2003). The infarcts and WMLs are expected consequences of small vessel disease. A subcortical cognitive syndrome is the cardinal clinical manifestation in SIVD attributed to preferential damage to the prefrontal–subcortical circuits (Cummings, 1993; Erkinjuntti *et al.*, 2000). Clinically, small vessel dementia is characterized by the subcortical cognitive syndrome plus pure motor hemiparesis, bulbar signs and dysarthria, gait disorder, variable depressive illness, emotional lability, and deficits in executive functioning. Neuroimaging patients with SIVD reveals multiple lacunaes and extensive WMLs, supporting the importance of imaging in the diagnostic criteria (Erkinjuntti *et al.*, 2000).

The early cognitive syndrome of SIVD is characterized by a dysexecutive syndrome with slowed information processing, usually mild memory deficit and behavioral symptoms. The dysexecutive syndrome in SIVD includes impairment in goal formulation, initiation, planning, organizing, sequencing, executing, set-shifting and set maintenance, as well as in abstraction (Cummings, 1994). The memory deficit in SIVD is usually milder than in AD, and is characterized by impaired recall, relative intact recognition, less severe forgetting and better benefit from cues. Behavioral and psychological symptoms in SIVD include depression, personality change, emotional lability and incontinence, as well as inertia, emotional bluntness, and psychomotor retardation.

Earlier phases of SIVD may include episodes of mild upper motor neuron signs (drift, reflex asymmetry, incoordination), gait disorder (apractic–atactic or small-stepped), imbalance and falls, urinary frequency and incontinence, dysarthria, dysphagia as well as extrapyramidal signs such as hypokinesia and rigidity (Roman *et al.*, 2002). However, these focal neurological signs are often subtle.

Strategic infarct dementia

Depending on the precise location, the time course and clinical features of strategic infarct dementia are highly variable. Strategic infarct dementia is characterized by focal, often small, ischemic lesions involving specific sites critical for higher cortical functions. The cortical sites include the hippocampal formation, angular gyrus and cingulate gyrus. The subcortical sites leading to impairment are the thalamus, fornix, basal forebrain, caudate, globus pallidus and the genu or anterior limb of the internal capsule (Erkinjuntti and Hachinski, 1993; Tatemichi, 1990).

Diagnostic criteria

Clinical criteria

The most widely used criteria for VaD include DSM-IV, ICD-10, the ADDTC criteria (Chui *et al.*, 1992) and the NINDS-AIREN criteria (Roman *et al.*, 1993).

The NINDS-AIREN criteria have been the most widely used criteria in randomized clinical trials. They:

- emphasize the heterogeneity of VaD syndromes and pathological subtypes, including not only ischemic stroke but other causes of CVD such as cerebral hypoxic ischemic events, white matter lesions and hemorrhagic strokes;
- recognize the variability in clinical course, which may be static, remitting or progressive;

- highlight the question of the location of ischemic lesions and the need to establish a causal relationship between vascular brain lesions and cognition;
- recognize the need to establish a temporal relationship between stroke and dementia onset;
- include specific findings early in the course that support a vascular rather than a degenerative cause;
- emphasize the importance of brain imaging to support clinical findings; and
- recognize the value of neuropsychological testing in documenting impairments in multiple cognitive domains.

Sensitivity of the criteria: the NINDS-AIREN criteria treat VaD as a syndrome with different causes and different clinical manifestations, not as a single entity, and list possible subtypes to be used in research studies. The focus is on consequences of CVD, but different causes are also taken into account. The criteria incorporate different levels of certainty of the clinical diagnosis (possible, probable, definite).

In a neuropathological series, sensitivity of the criteria for probable and possible VaD was 58% and specificity 80% (Gold *et al.*, 1997). The criteria succesfully excluded AD in 91% of cases, and the proportion of combined cases misclassified as probable VaD was 29%. Compared with the ADDTC criteria, the NINDS-AIREN criteria were more specific and they excluded combined cases better (54% vs. 29%). In a more recent series, the sensitivity of NINDS-AIREN criteria for probable VaD was 20% and specificity 93%; the corresponding figures for probable ADDTC were 25% and 91% (Gold *et al.*, 2002). The inter-rater reliability of the criteria is moderate to substantial (k 0.46–0.72) (Lopez *et al.*, 1994).

Alzheimer's disease with CVD

AD and CVD co-exist in a large proportion of patients (Kalaria and Ballard, 1999). Such patients may present clinically either as AD with evidence of cerebrovascular lesions on brain imaging, or with features of both AD and VCI (Rockwood *et al.*, 1999). It remains a major clinical undertaking to distinguish dementia due to AD from that arising from CVD in view of the considerable overlap. Both result in cognitive, functional and behavioral impairments. There are also shared pathophysiological mechanisms (e.g. WMLs, delayed neuronal death and apoptosis) (Pantoni Garcia, 1997; Skoog *et al.*, 1999; Snowdon *et al.*, 1997), associated risk factors (e.g. age, education, arterial hypertension) (DeCarli, 2004; Skoog *et al.*, 1999) and neurochemical deficits including cholinergic neuronal dysfunction (Roman and Kalaria, 2006; Wallin *et al.*, 2002). Based on the findings from the Nun Study (Snowdon *et al.*, 1997), it has been further suggested that CVD may play an important role in determining the presence and severity of clinical symptoms of AD. Either way, the prevalence of AD with CVD appears grossly underestimated (Kalaria and Ballard, 1999; Langa *et al.*, 2004).

The diagnosis of mixed AD and CVD is a challenge. Accumulating evidence shows that different vascular factors, including hypertension and stroke, increase the risk of AD, and frequently CVD co-exists with AD (de la Torre, 2004; DeCarli, 2004; Kalaria and Ballard, 1999; Skoog *et al.*, 1999). This overlap is increasingly important in the oldest (>85 years of age) populations. Clinical recognition of patients with AD and CVD is problematic as is evident from the neuropathological series of Moroney *et al.* (1997) and others (Neuropathology Group, 2001). These patients exhibit a history of vascular risk and a sign of CVD providing a clinical picture that is close to VaD. However, fluctuating course (Odd ratio; OR=0.2) and history of strokes (OR=0.1) were the only items differentiating AD from AD with CVD.

Some of the challenging clinical scenarios include the developing AD in patients with post-stroke dementia, and VaD patients with an insidious onset or a slow progressive course. AD with CVD can present clinically either as AD with evidence of vascular lesions upon brain imaging, or with clinical features of both AD and VaD (Rockwood *et al.*, 1999). In a Canadian study, typical AD presentations with one or more features pointing to "vascular aspects" derived from the Hachenski Ischemic Scale (HIS) were used successfully to diagnose AD plus CVD in combination with the neuroimaging of ischemic lesions (Rockwood *et al.*, 2000). Vascular risk

factors and focal neurological signs were present more often in AD with CVD than in "pure" AD. Other clinical clues for a diagnosis of AD with CVD were gained from analyses of disease course characteristics and presentations of patchy cognitive deficits, early onset of seizures, and gait disorder.

A better solution to recognizing patients with AD plus CVD would be to discover reliable biological markers of clinical AD. Other potential markers include early prominent episodic memory impairment, early and significant medial temporal lobe atrophy on MRI, bilateral parietal hypoperfusion on single photon emission computed tomography, and low concentrations of CSF Aβ peptides with high tau-protein.

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2

Vascular cognitive impairment: prodrome to VaD?

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Introduction

Dementia is a public health problem, particularly affecting those over age 80 (Evans *et al.*, 1989; Hebet *et al.*, 2001). While Alzheimer's disease (AD) is the most common cause for dementia among older individuals (Evans *et al.*, 1989; Sayetta 1986), the lifetime risk for stroke equals and may exceed the risk of AD in some circumstances (Seshadri *et al.*, 2006). In addition, MRI evidence of asymptomatic cerebrovascular disease (CVD) occurs in one-third of older individuals (DeCarli *et al.*, 2005). It is, therefore, not surprising that concurrent CVD is often seen in older dementia patients even though they may have a slowly progressive dementing illness most consistent with AD (Mungas *et al.*, 2001b). Although research in this area is ongoing, the impact of clinically silent CVD on cognition and the interaction between CVD and AD processes remains incompletely understood. In this chapter, we discuss the potential role that vascular risk factors and asymptomatic CVD may have on lifetime risk for dementia. In particular, we hypothesize that asymptomatic CVD – in contrast to stroke or other forms of symptomatic CVD – acts as a susceptibility factor for the expression of dementia, most commonly due to AD.

Vascular cognitive impairment defined

As our understanding of the relationship between vascular disease and cognition continues to evolve, so does our terminology. In this light, vascular dementia (VaD) is now considered to be the extreme end of a spectrum of syndromes of vascular cognitive impairment (VCI) (Hachinski, 1992). As such, the concept of VCI encompasses all forms of cognitive impairment associated with CVD, ranging from subtle impairments in otherwise cognitively normal individuals through mild cognitive impairment to dementia (O'Brien *et al.*, 2003). VCI also encompasses dementias where both CVD and AD processes are thought to co-occur (O'Brien *et al.*, 2003). Finally, it is important to stress the difference between VCI and VaD. For the diagnosis of VaD, CVD is assumed to be the sole cause for the dementia. Although VaD may result from many forms of CVD, VaD is most clearly delineated by the presence of symptomatic CVD, usually due to stroke, in association with stepwise declines in cognition (Roman *et al.*, 1993) or evidence of multiple, bilateral gray matter infarcts (Knopman *et al.*, 2003). In contrast, VCI is a term used mostly for individuals who do not fulfill all the specified criteria for dementia and for whom the

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