Review

Beyond mild cognitive impairment: vascular cognitive impairment, no dementia (VCIND)

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Abstract

Identifying the causes of dementia is important in the search for effective preventative and treatment strategies. The concept of mild cognitive impairment (MCI), as prodromal dementia, has been useful but remains controversial since in population-based studies it appears to be a limited predictor of progression to dementia. Recognising the relative contribution of neurodegenerative and vascular causes, as well as their interrelationship, may enhance predictive accuracy. The concept of vascular cognitive impairment (VCI) has been introduced to describe the spectrum of cognitive change related to vascular causes from early cognitive decline to dementia. A recent review of this concept highlighted the need for diagnostic criteria that encompass the full range of the VCI construct. However, very little is known regarding the mildest stage of VCI, generally termed 'vascular cognitive impairment, no dementia' (VCIND). Whether mild cognitive change in the context of neurodegenerative pathologies is distinct from that in the context of cerebrovascular diseases is not known. This is key to the definition of VCIND and whether it is possible to identify this state. Distinguishing between vascular (that is, VCIND) and non-vascular (that is, MCI) cognitive disorders and determining how well each might predict dementia may not be possible due to the overlap in pathologies observed in the older population. Here, we review the concept of VCIND in an effort to identify recent developments and areas of controversy in nosology and the application of VCIND for screening individuals at increased risk of dementia secondary to vascular disease and its risk factors.

Introduction

A better understanding of dementia, including its causes, underlying pathophysiological processes and earliest possible identification, has become a major public health priority. Changes in cognition associated with age are complex, especially with regard to distinguishing usual from pathological brain ageing. Multiple and often intertwined pathological factors, including atrophy, neurodegeneration, inflammation, stroke and genetic-related factors, cause dementia [1]. Here, we explore the link between vascular disease, cognitive decline and dementia risk. Given the relatively high proportion of dementia attributable to possibly reversible midlife vascular causes [2], it has been suggested that vascular risk manipulation may result in up to a 50% reduction in the forecasted dementia prevalence rate in individuals who are 65 years old or older [3,4]. Vascular risk factors for dementia may also contribute to impairments observed in the pre-clinical stage of cognitive decline. This has raised questions regarding (a) whether vascular disease can predict cognitive change and dementia risk in otherwise non-impaired individuals and (b) the duration and possible reversal of cognitive symptoms and dementia depending on vascular disease manipulation and treatment. The aim of this review is to describe the current understanding of the division between pre-clinical cognitive impairment in the context of vascular disease versus the absence of vascular disease. The focus will be on the term 'vascular cognitive impairment, no dementia' (VCIND), an umbrella term that broadly encompasses cognitive deficits associated with vascular disease which fall short of a dementia diagnosis, in order to determine whether within the context of this condition there is a pre-clinical state linked to a high risk of dementia progression.

Age-related changes in the vascular system

Ageing in the developed world is associated with changes in the vascular system which result in atherogenesis, increased pulse pressure and increased risk of developing vascular disease as a consequence of a direct effect on the vascular system (for example, arterial hypertension and vasculitis) or

AD = Alzheimer disease; A-MCI = anmestic subtype of mild cognitive impairment; MCI = mild cognitive impairment; VaD = vascular dementia; VCI = vascular cognitive impairment; VCIND = vascular cognitive impairment, no dementia.

indirect metabolic and haemodynamic effects secondary to other disorders (for example, diabetes, congestive heart failure and obesity) [5]. Vascular disease can reduce cerebral perfusion, causing oxidative stress and neurodegeneration [6]. Vascular disease has also been reported to accelerate atrophy and result in white matter abnormalities, asymptomatic infarct, inflammation and reduced glucose metabolism, cerebral blood flow and vascular density [5,7]. Such pathological changes have been associated with not only dementia of the vascular type but also Alzheimer disease (AD) [8,9]. The mechanisms by which vascular disease and its risk factors cause pathology and how such changes impact cognitive function are incompletely understood but are thought to depend on age, disease co-morbidity, lifestyle and genetic susceptibility and predisposition. An important question is whether different vascular disease factors can be separated from each other and from the effect of ageing itself in order to identify their unique impact on cognitive function. A more complete understanding of the relationship between vascular disease, cognitive decline and dementia risk will have important implications in identifying vulnerable population subgroups and a potential treatment target.

Classification systems of early cognitive change

Age-related cognitive change can be placed along a continuum from normal to severely demented, with intermediate stages of cognitive decline. To date, there is no consensus on where boundaries between disease and non-disease lie, if such a definite boundary exists. Rather than a strict dichotomisation, the determination of impairment may instead be based on the likelihood or probability that ageing is not occurring in accordance with normative expectations. Furthermore, classification systems of cognitive change themselves raise questions regarding the level of cognitive and functional dysfunction used to reliably categorise individuals and those risk factors apart from ageing itself that contribute to mild and severe cognitive change.

Mild cognitive impairment

The term mild cognitive impairment (MCI) broadly defines an intermediate state of cognitive decline, predominately linked to impaired memory function, which is thought to be predictive of dementia, primarily AD. Various definitions have been proposed in the literature, each with differences in focus (for example, age-associated change versus pathological decline) and diagnostic criteria (for example, memory versus non-memory impairment) [10-14]. As a possible tool for identifying individuals at increased risk of dementia, MCI is an important concept. Indeed, in clinical samples, individuals with a case diagnosis of the anmestic subtype of MCI (A-MCI) [15-17] have been found to progress to dementia at a rate of 10% to 15% per year compared with a progression rate of only 1% to 2% in normal controls [18,19]. In contrast, in the general population, the positive predictive validity of A-MCI is poor [19]. Many incident dementia cases are found to be excluded from an A-MCI case diagnosis, and of persons with A-MCI, many remain stable or revert to normal cognitive status at follow-up [10]. These findings are consistent across all MCI definitions (for example, amnestic versus non-amnestic and single- versus multiple-domain MCI) [19].

No MCI criteria can be recommended for population screening of individuals at high dementia risk [20]. This raises a number of questions regarding the precision and utility of current diagnostic criteria and what the best indicators of dementia risk are and whether these are being captured in current diagnostic methods. Poor predictability possibly results from limitations in case findings due to a lack of clinical judgement and inflexibility in operationalisation of criteria when a diagnosis of MCI is made outside the clinical setting. However, it has been suggested that MCI predictability may be improved through consideration of the underlying pathogenesis of cognitive decline [21]. Sub-classification of MCI with and without co-morbid vascular disease may therefore be important for discriminating individuals at high versus low dementia risk in the general population.

Although the fact is not always explicitly stated in MCI-defining criteria, an MCI case diagnosis is usually made following the exclusion of individuals with psychiatric and vascular co-morbidity [10,12,22]. As such, the association between vascular disease and MCI is not widely studied. Where vascular disease has been evaluated in the context of MCI, no clear pattern between vascular disease and incident MCI or between vascular disease, MCI and risk of dementia progression has been found. An increased risk of incident MCI has been associated with elevated midlife blood pressure [23], elevated total cholesterol level [23], history of coronary artery bypass grafting [24], stroke [25] and midlife hypertension [21] in some, but not other [26], studies. Only atrial fibrillation and low folate levels have been associated with an increased risk of dementia progression from MCI [27]. Inconsistencies in conclusions possibly result from differences in patient sources (for example, clinic- versus population-based), type of impairment (for example, narrow [A-MCI] versus global measures of cognitive impairment as captured in the term 'cognitive impairment, no dementia' [CIND]), definitions of disease and measurement of vascular factors over varying time frames and with instruments of different sensitivities (for example, subjective report versus objective measure). To better identify the link between vascular disease and cognitive impairment, the term vascular cognitive impairment (VCI) was introduced [9,28-32].

Cognitive impairment and vascular disease

VCI refers to cognitive decline attributable to vascular disease. However, unlike MCI (which is a narrow term capturing a pre-clinical form of dementia), VCI encompasses individuals affected with any degree of cognitive decline caused by or associated with vascular disease and its risk

factors. As such, the level of impairment in VCI ranges in severity from mild to vascular dementia (VaD) or mixed VaD, in which cerebrovascular and AD pathologies co-occur. Calls for more specific staging have recently led to further sub-classification of VCI to capture vascular disease-related impairment not fulfilling criteria for dementia. This stage is defined using the term VCIND and has been further subdivided to include specific terms for pre-clinical impairment, including vascular MCI (V-MCI), MCI of vascular type, pre-clinical VCI, vascular pre-dementia MCI and mild VCI (M-VCI/MCI-vas) [29]. Each is analogous to the concept of MCI in terms of stage. However, similar to MCI, VCIND and its component states lack consistent standardised indicators (for example, symptoms) and a unique case definition.

Whether within VCIND there is a state predictive of dementia is largely unknown. Commonly, VCIND is not seen as a pre-clinical dementia state. Where longitudinal outcome across the spectrum of VCI has been investigated, progression is not always clinical (that is, decline/dementia), with many cases improving or remaining stable at follow-up [9,33-35]. Predictive ability may depend on the nature of the vascular disturbance in addition to methodological factors (for example, case description, sample and nature of cognitive impairment). As with MCI, terminology and diagnostic criteria for VCIND have not been harmonised, making cross-study comparison of disease outcomes difficult. Yet unlike MCI, in which algorithms have been created for each different classification [10], no such algorithm yet exists for VCIND and its many possible subtypes.

Defining the boundary between VCIND and MCI

Some MCI classifications do not consider possible vascular contributing factors to cognitive impairment, and therefore the distinction between MCI and VCIND becomes blurred [36]. This raises questions of the benefit in distinguishing MCI from VCIND and whether formulating a new diagnostic category such as VCIND is even necessary. Whether vascular disease is considered in the diagnosis of MCI may influence general population prevalence estimates and longitudinal patterns of progression. Empirical evidence as to the degree of co-morbidity across different pathologies (including, for example, AD and VaD pathologies) will help new classifications, particularly as biomarkers of specific pathologies emerge.

Generally, the differential diagnosis between MCI and VCIND is clinical and based on the distinction between AD and VaD. AD is characterised by a steady and progressive loss of memory and cognitive faculties, including language deterioration, impaired visuospatial skills and poor judgement [37]. AD has a distinct neuropathological pattern of beta-amyloid plaques and neurofibrillary tangles [38,39]. Other significant correlates of cognitive decline include synaptic loss, neuronal death and disruption to the cholinergic pathway [40]. In contrast, the disease course of VaD is highly variable, generally following a stepwise pattern of decline and fluctuating course [41,42]. For a diagnosis of VaD, it is recommended that radiographic features of vascular disease, including evidence of an ischaemic lesion, white matter hyperintensities and/or hypometabolism, be confirmed [37]. However, in some cases, AD and VaD have been found to result in similar cognitive, functional and behavioural disturbances, and frequently both pathologies co-occur [43-45]. AD and VaD may share associated risk factors (stroke, arterial hypertension, increasing age and low educational attainment), structural changes, neuropathological profiles (white matter lesions and apoptosis) and neurochemical changes (that is, in the cholinergic system) [46]. Overlap may also result from the large degree of silent risk pathology in older people.

In older people, multi-morbidity is common and a strict dichotomisation between degenerative and vascular dementing disorders at both pre-clinical and dementia stages is difficult to undertake, possibly artificial and perhaps not the most useful approach. Below, we explore the cognitive, neuroimaging and neuropathological profiles of MCI and VCIND to determine whether evidence exists for the separation of both conditions.

Cognitive differences (MCI with vascular disease versus MCI without vascular disease)

Neuropsychological studies have identified attentional-executive deficits and psychomotor slowing, with relatively preserved language and recognition memory in individuals with vascular disease [47,48]. However, not all studies agree on the importance of each cognitive domain and no single deficit or pattern of deficits as yet accurately signals an underlying vascular cause [49]. This is not unexpected given the multiplicity of aetiologies for vascular disease and the fact that the pattern and extent of cognitive deficits would likely reflect not only disease type, but also its severity [50,51]. For example, cognitive impairment as a consequence of stroke would likely depend on not only timing and the anatomical location of the stroke, but also the laterality, severity and extent of the lesion. Furthermore, impairments in attention and executive and motor function are not necessarily restricted to vascular causes of dementia and have also been associated with Lewy body dementia [52] and fronto-temporal dementia [53].

Where VCIND has been followed longitudinally, cognitive impairment associated with memory (free and cued recall) and category fluency was found to predict risk of incident dementia [54]. These findings suggest that the pattern of impairment in VCIND conforms more to AD than to VaD. Indeed, almost half of the cases progressed to AD or mixed AD at 5 years of follow-up. However, whether these findings extend across the different vascular causes of VCIND (that is, stroke- versus hypertension-related cognitive impairment) and other cognitive domains (that is, perception and motor performance) remains to be tested.

With regard to MCI, no consistent cognitive profile exists across the many different case definitions. The focus of MCI is predominantly impaired memory, but deficits in other cognitive domains will also be observed when, by definition, they are also included [55]. Subdivisions between different cognitive subtypes of MCI (for example, amnestic versus non-amnestic and single- versus multi-domain) have implications for inference about aetiology and outcomes. Indeed, while A-MCI [15,16,56] is thought to be a precursor of AD, non-amnestic subtypes of MCI have been found to identify individuals at high risk of both AD and VaD [57].

Where the cognitive profile of individuals with MCI and co-morbid vascular disease has been compared with that of individuals with MCI and no vascular disease, group differences have been reported in some [58,59], but not all [60], studies. Where differences have been observed, the MCI vascular group shows more extensive cognitive impairment primarily in speed, attention and executive function [58], consistent with the general pattern of cognitive difficulties resulting from vascular disease alone [29]. In other studies, vascular pathology in MCI (for example, white matter lesions) has been associated with decreased risk of progression of cognitive pathology and a more stable cognitive change profile [61,62], although this is not always replicated [63]. These findings suggest a complex relationship between vascular disease and cognitive progression in MCI which might relate to the specific vascular disease factor. Of importance is determining whether the presence of vascular disease accelerates or intensifies the cognitive disturbance in all cases of MCI and which factors might mediate this relationship (for example, age and reserve). The specific type of cognitive impairment associated with vascular disease needs to be defined and measures that are sensitive, specific and appropriate for longitudinal and observational assessment of cognition in the context of vascular disease (that is, memory versus non-memory domains) need to be identified in order to facilitate the development of diagnostic criteria for cognitive decline in the presence (VCIND) versus the absence (MCI) of vascular disease.

Neuroimaging profile (MCI versus VCIND)

Neuroimaging in VCIND shows a pattern of vascular lesions that are similar to, but less severe than, changes observed in VaD [64]. Pathology includes evidence of leukoaraiosis and white matter infarction [28,65,66], with mild hippocampal and enthorhinal cortex atrophy relative to the level seen in MCI/AD [64]. In contrast, neuroimaging in MCI generally shows a pattern of changes similar to that observed in AD, namely temporal and hippocampal atrophy, reduction in whole-brain glucose metabolism and white matter degeneration, including hyperintensities and white matter lesions identified using diffusion tensor imaging [67-74]. Development of dementia from MCI has been associated with hippocampal volume changes [69,75-79], medial temporal lobe atrophy [80] and metabolic alteration [78,81].

Although neuroimaging studies of VCIND and MCI suggest different pathological processes, findings are not always consistent and such changes are imperfect predictors of disease. Considerable intra-individual variation exists, and overall, neuroimaging-identified abnormalities correlate poorly with cognitive profile [43]. Indeed, such changes have also been observed in individuals who do not exhibit cognitive deficits, raising questions about the uniqueness of findings [82]. Inconsistency in results possibly arises due to differences in the use of subjective visual rating scales to assess the extent of pathology across groups, regional focus of disease (global versus focal), in addition to differences in enrolment criteria and the type and severity of vascular disease across imaging cohorts. Indeed, different vascular disease factors are associated with varying types and levels of pathology: hypertension has been associated with reduced cerebral blood flow [83] and an increased risk of periventricular white matter lesions [84,85]; lower arterial oxygen saturation and chronic obstructive pulmonary disease have been associated with cerebral white matter lesions, but not lacunar infarcts [86]; diabetes has been associated with cortical and hippocampal atrophy [87,88], white matter lesions [89] and lacunar infarcts [89]; and current smoking status, diabetes and hypertension are associated with both neurodegenerative (that is, decreased brain volume) and vascular (that is, lacunar infarcts and white matter lesions) changes [90].

The severity and type of lesions required for a diagnosis of MCI and VCIND remain controversial. Vascular disease and its risks are associated with brain changes but the clinical relevance of such changes in the prediction of cognitive decline and dementia progression remains uncertain. Isolating unique disease effects from the effects of ageing and other risk factors (that is, genetic susceptibility) will be important in determining cellular/molecular/functional vulnerability as a consequence of vascular disease as well as establishing with accuracy those changes that distinguish who will and will not develop cognitive decline and subsequent dementia.

Neuropathology profile (MCI versus VCIND)

The neuropathological profile of MCI has been derived mainly from a relatively small number of studies with MCI defined predominately using the A-MCI subtype. Compared with highly selected controls, MCI cases generally show an increase in neurofibrillary tangle pathology in memory-related cortical regions, including the entorhinal cortex, fusiform gyrus and temporal pole [91,92]. These changes are thought to represent one of the earliest pathological substrates of this condition [93] and have been taken to suggest that many MCI cases are early or prodromal AD [94,95]. Vascular pathology has also been reported in MCI such that the neuropathology of some cases includes features associated with both AD and VaD [96]. However, there is considerable heterogeneity in findings and not all individuals with MCI at death or those who progress from MCI to dementia have been reported to show any particular neuropathology [97].

Rather, they have been indistinguishable from control groups. Inconsistency in outcome may arise from differences in study population (for example, specialised clinic versus population), age group differences (that is, young-old versus old-old), operational definition of MCI and neuropathological criteria (for example, Khachaturian, Consortium to Establish a Registry for Alzheimer's Disease, or National Institute on Aging-Reagan).

Whether there is a consistent neuropathological profile across the spectrum of vascular causes and severity levels of VCI is unknown but seems unlikely. Indeed, VCI is a multifactor disorder related to a wide variety of lesions and causes and as such the pathological profile, similarly to the psychological and radiological profiles, would be expected to be heterogeneous. In autopsy studies, an increased prevalence of cerebral vascular pathology has been found in individuals with stroke [98], diabetes mellitus [99,100], angina (with comorbid dementia) [101,102] and hypertension [103]. Pathological features have included large- and small-vessel disease, gliosis, microvascular brain damage (severe cribriform change), white matter damage, microinfarction and haemorrhage [104]. Cardiovascular risk factors have also been associated with AD-like neuropathological lesion formation in some, but not all, studies, with the extent of pathology typically being more severe in APOE (apolipoprotein E) e4 carriers [100,103,105-107]. In contrast, in other cases, an inverse association between vascular disease and the extent of cerebral degenerative pathology has been found [101]. The profile of pathology across the different vascular disease factors is heterogeneous and the significance of such changes in the development of cognitive impairment is not known. Furthermore, neuropathological associations appear to be risk factor-specific and population-specific, being absent when vascular disease is assessed using composite cerebrovascular index scores and in non-Caucasian populations [108,109].

Across the spectrum of age-associated brain changes, no neuropathological profile yet exists that reliably distinguishes impairment of different severity levels and causes. In the general population, currently identifiable pathological features have not been found to correlate well with observed clinical and cognitive profiles: many non-demented healthy controls also show evidence of pathological brain changes associated with both AD and VaD [43,110,111]. Techniques that better characterise the impact of vascular disease on brain structure and more sensitive measures for accurately staging cognitive status which incorporate known risk factors are needed for diagnostic differentiation between an *at-risk* and a *not at-risk* brain. However, as with AD, expecting neuropathology to be a gold standard at any given age for the diagnosis of VCI is an oversimplification [112].

Vascular risk factor control

Current pharmacological and non-pharmacological modifications of vascular disease and its risks have been found to have only a marginal effect on reducing dementia prevalence in the general population [113]. Indeed, most strategies, whether pharmacological or non-pharmacological, are ineffective in the prevention of dementia and are potentially harmful. With regard to MCI, while pharmacological and lifestyle modifications have been found to be effective in ameliorating cognitive impairment in selected older cohorts [114,115], no consistently positive results have emerged from randomised controlled trials for such manipulation in the prevention of MCI or future dementia progression in older people in the general population [116,117]. Where the primary prevention of VCIND has been considered, physical activity has been found to reduce the risk of VCIND in women, but not men [118]. Why gender differences emerged in this study is unclear but is thought to be linked to gender reporting bias in physical activity levels or to statistical error (type 2 error) due to the small number of male cases. However, before recommendations based on this result can be made, it must be replicated in population-representative samples using objective measures of physical activity.

Overall, the results of intervention trials of vascular risk reduction on the prevention of cognitive decline and dementia have not been encouraging so far. There are, however, other reasons why cardiovascular and cerebrovascular disease should be prevented and treated, especially for the prevention of recurrent stroke and hypertension, which themselves are strong risk factors for functional impairment and mortality [119]. Further trials are needed to determine whether the manipulation of different vascular diseases and vascular risk factors prevents VCIND and dementia progression. However, it is unlikely that a single strategy will cure or prevent all dementia; rather, early treatment may require a combination of therapies with different targets and time frames for instigation (that is, early, mid- and later life).

Future directions

A more complete understanding of the relationship of vascular disease to cognitive decline and dementia risk is needed. Even when vascular pathology appears to be the main underlying process, the effect can be heterogeneous, with diverse neuropsychological, clinical, radiological and morphological profiles, often in the presence of other pathologies. To date, the risk of dementia progression cannot yet be accurately predicted from pre-dementia states captured in the concepts of MCI and VCIND. Cognitive decline can also occur prior to vascular insult (for example, pre-stroke dementia), raising the question of causality [1]. How vascular disease relates to dementia and its influence across an individual's life span and the unique and interactive mechanisms of action on neurodegeneration must be investigated further to identify the best treatment and preventative target.

Conclusions

Before case screening for individuals at high risk of dementia secondary to vascular disease can be undertaken, the

concept of VCIND will require evidence-based consensus criteria and validation as a pre-clinical state that confers high dementia risk in both clinical and population-based studies. Many questions remain open, particularly with regard to identifying where the state of VCIND begins and ends. This review suggests that cognitive change would be expected to be influenced by vascular disease type and severity, disease onset, co-occurring factors, underlying vulnerability (for example, age, education and genetics) and whether pathology occurs secondary to another process (for example, AD). Accurate early detection of the general population at increased risk of dementia is central for the implementation of interventions to prevent dementia and other memory-related problems in older individuals.

Competing interests

The authors declare that they have no competing interests.

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