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The assessment of cognitive and behavioural disturbances in vascular cognitive impairment (VCI) — recommendations of an expert working group

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ABSTRACT

With newer research-based classification systems, the term Vascular Cognitive Impairment (VCI) is now preferred to vascular dementia. VCI is an umbrella term that includes all forms of cognitive deficits ranging from mild cognitive impairment of vascular origin (VaMCI) to vascular dementia (VaD).

The new VCI construct takes into account the fact that in addition to single strategic infarcts, multiple infarcts, and leukoaraiosis, there are other mechanisms of cerebrovascular disease such as chronic hypoperfusion that might account for the pattern of cognitive deficits associated with vascular dementia. The key to defining the spectrum of VCI is neuropsychological testing, bedside or office-based clinical examination, and neuroimaging. The lack of specific cognitive tools that are sufficiently sensitive to detect subtle deficits makes the assessment of cognitive impairment difficult. Prospective cross-sectional and longitudinal studies of VCI from different settings are therefore required.

Although there have been few published reports, behavioural and psychological symptoms (BPS) are inherently present in VCI from the onset and during the course of the disease. Besides the type of population (i.e. clinical, community or nursing-home settings), the definition of VCI/VaD and the instruments used, and differences in the prevalence and pattern of BPS between various studies, could be due to other, often unconsidered, factors such as gender, age, education, use of medication and VCI/VaD severity.

Key words: vascular dementia, mild cognitive impairment, stroke, cerebrovascular disorders, cognition, behaviour, dementia, multi-infarct, mixed dementia

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Introduction

The construct 'vascular cognitive impairment' (VCI) was introduced to comprise a heterogeneous group of cognitive disorders that share a presumed vascular cause; this includes both dementia and cognitive impairment without dementia. The most severe form of VCI is vascular dementia (VaD), and new subtypes with milder cognitive symptoms such as vascular mild cognitive impairment (i.e. VaMCI) are gradually being defined. The new VCI construct takes into account the fact that in addition to single strategic infarcts, multiple infarcts, and leukoaraiosis, also chronic hypoperfusion might account for the pattern of cognitive deficits associated with VaD. Hence, VCI is an umbrella term that includes all forms of cognitive deficits ranging from VaMCI to VaD [1, 2]. Different magnetic resonance imaging techniques remain crucial for the determination of vascular pathology using both well-established [3] and more innovative approaches [4].

VCI is used for all forms of cognitive disorder associated with cerebrovascular disease (CVD) regardless of the pathogenesis (e.g. cardioembolic, atherosclerotic, ischaemic, haemorrhagic, genetically-related CVD, and even potential interactions with Alzheimer's Disease [AD] and other so-called neurodegenerative disorders). The VCI construct has also brought greater attention to to opportunities for prevention, early intervention, and the coexistence of AD pathology [5].

An overview of the neurobiological aspects of VCI that may be relevant to its management is beyond the scope of this paper, and in any case was recently thoroughly analysed in the consensus report by Bordet et al. [6].

Over the last decade, by recognising that only about half the population of patients with cerebrovascular pathology exhibit full blown dementia, the term VCI has become more appropriate to describe the whole spectrum of cognitive-behavioural deficits due to cerebrovascular pathology. Different approaches have been proposed for the classification of VCI, but no particular criteria set has gained universal acceptance. The five most common criteria sets are: the DSM-5 [7]; the International Classification of Diseases, 11th Ed (ICD 11) [8]; the State of California Alzheimer's Disease Diagnostic and Treatment Centres (ADDTC) criteria [9]; the National Institute of Neurological Disorders and Stroke with the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria [10]; and VASCOG [11]. Although NINDS-AIREN and ADDTC are not fundamentally different, the latter do not include haemorrhagic and anoxic lesions. VASCOG criteria correspond to DSM-V [12].

Aim of the study

Understanding of the cognitive and behavioural aspects of VCI and their clinical assessment is still insufficient.

This paper was aimed at reviewing published data on cognitive and behavioural disturbances through the whole spectrum of vascular cognitive impairment in order to propose a set of clinically accepted and valid testing procedures that could be used to identify patients with possible cognitive and/ /or behavioural disturbances in generic as well as in specialised neurological settings.

By doing so, pertinent literature (excluding case studies) published in PubMed and MEDLINE (containing the search items "vascular dementia" OR "vascular cognitive impairment" AND "neuropsychology" OR "cognition" between 1990 and 2020 was identified and reviewed by the workgroup. Our workgroup focused mainly on identifying diagnostic approaches applicable in different settings, as most other consortia or task-forces aim to improve the diagnosis and treatment of VCI [13] through standardising assessment and treatment approaches that seem to be based mainly on resources available from inpatient stroke units.

As discussed above, the terminology related to VCI and VaD has changed over the years. According to O'Brien et al., vascular dementia itself has the following subtypes: multi-infarct dementia, small vessel dementia, strategic infarct dementia, hypoperfusion dementia, haemorrhagic dementia, hereditary vascular dementia and mixed dementia [1]. VaD may be also divided into subcortical (sVaD) and cortical (cVAD) [14]. Unfortunately, only in some of the studies has the clinical cohort been defined in line with this terminology. Also, we did not limit our search on VCI to dementia cohorts. Whenever available, when describing study results, we used more specific terms.

Epidemiology of VCI

Vascular disease is a major cause of cognitive impairment and dementia, but is under-investigated and poorly characterised compared to Alzheimer's Disease (AD). Depending on the age cohorts under study, the prevalence estimates of VaD can vary substantially, generally showing an exponential increase in prevalence and incidence as age increases. These estimates seem to mirror the pattern of stroke, though dementia after stroke may be more frequent in the very elderly. Thus, while the World Federation of Neurology Dementia Research Group [15] has estimated VaD in developing countries to be in the range between 0.6% and 2.1%, a pooled analysis of European population-based studies reported VaD to be prevalent in 1.6% of subjects over the age of 65, with substantial variation in 5-year age-specific prevalence rates. While some studies were able to show a higher incidence of VaD in men than in women [16], a pooled analysis of incidence studies found no sex differences [17]. Similarly to Western countries, AD is the leading cause of dementia in Asian populations. The prevalence of AD doubles every 4.3 years, whereas the prevalence of vascular dementia (VaD) doubles every 5.3 years. Recent reports from China have suggested that previous estimates of the dementia burden, based on smaller datasets, might have underestimated the burden of dementia in China to date [18].

As indicated by a recent study in which dementia diagnosis was established on the basis of a cognitive screening (Montreal Cognitive Assessment, MoCA) three months after middle cerebral artery territory ischaemic stroke, dementia may be present in about 25% of cases [19]. Thus the frequency of VaD diagnosis could be be both underestimated and overestimated if patients with focal language and cognitive deficits are not neuropsychologically assessed.

The heterogeneity of the VCI construct (principally the inclusion of the vascular variant of mild cognitive impairment, VaMCI) creates challenges for descriptive epidemiology, much of which still refers to VaD terminology. In the Canadian Study of Health and Aging, it was estimated that approximately 5% of people over the age of 65 had VCI, with 2.4% having VaMCI, 0.9% having mixed dementia, and 1.5% having VaD [20]. Gorelick et al. [5] and Rincon and Wright [21] report the overall prevalence of VaD to be 5-10% in people older than 65 years, and this increases rapidly thereafter,with a prevalence of as much as 50% of the population aged over 85.

Is there a neuropsychological 'fingerprint' of VCI?

VCI has both cognitive and behavioural manifestations. VaMCI is characterised by executive dysfunction, slowed information processing, episodic memory deficits, with mood and personality disorders. Although there were significant differences in all cognitive domains between VCI without dementia and healthy controls, deficits in processing speed, working memory and visuospatial construction were more prevalent [22]. In contrast to VaMCI, non-vascular MCI had a greater relative deficit in episodic memory [22].

As mentioned above, VCI can present with a variety of neurocognitive symptoms which can be relatively mild or more severe. Although this view has been challenged [23], there are many studies indicating the preponderance of mental slowing in combination with executive dysfunction. The presence of memory impairment (of amnestic type) is highly suggestive of an AD profile, while executive impairment may appear both in non-vascular MCI and VaMCI. When analysing assessment results in a particular patient, the presence and significance of executive impairment based on quantitative scores has to be interpreted in the context of qualitative features and memory functioning [24]. Executive tests, being the most complex neuropsychological measures, are likely to be failed due to factors other than true executive impairments.

The individual neuropsychological profile of VCI is highly dependent on the topography of the underlying vascular pathology, affecting either large or small vessels. If VCI is due to large vessel disease (LVD) and occurs post-stroke (sometimes referred to also as strategic infarct dementia), the neuropsychological profile is characterised mainly by focal deficits corresponding to the localisation of the stroke area (e.g. hemispatial neglect following an infarct in the right middle cerebral artery) (Tab. 1). In accordance with the overall clinical outcome, the severity of the neuropsychological sequelae differs according to different vascular incidents: worse for haemorrhagic than for ischaemic strokes, and less favourable for ruptures of arteriovenous malformations than for cerebral aneurysms [25].

Thalamic strokes are associated with the most heterogeneous clinical manifestations due to reciprocal connections with different cortical areas and several sources of vascular supply [26]. Similarly, strokes affecting the basal ganglia (termed silent lacunar infarcts) lead to various clinical manifestations, affecting mainly language, memory and executive functions [27].

VCI, in the absence of stroke, is characterised by slowed information processing, impaired working memory and executive functions, episodic memory impairment, and visuospatial deficits. Thus, the neuropsychological pattern of VCI is not specific to the underlying vascular deficit, but rather reflects the disconnection of cortico-limbic loops that may be affected either due to vascular or to neurodegenerative pathology [27]. Information processing, working memory and executive function recruit complex brain networks and the severity of their impairment is significantly correlated to white matter pathology [28].

Update on neuroimaging correlates of VCI

Recent literature suggests that the presence of cognitive impairment post-stroke may be more closely related to structural global network competence than to traditional vascular burden scores that were popular in previous years [29]. Deterioration in connectivity following vascular lesions seems to be the key to the development of cognitive impairment [30]. Also, novel MRI approaches show promise in differentiating between amnestic and non-amnestic VCI on the basis of single-shot T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence [31]. As the severity of so-called frontal deficits is associated with a haemodynamic pattern indicative of cerebral hypoperfusion and enhanced vascular resistance on transcranial doppler (TCD) [32], the use of TCD may become more popular, especially in the follow-up of VCI patients, because its cost is lower than MRI. However, the sensitivities of the two methods to change need to be established.

Lesions along association white matter tracts mediating intrahemispheric long-range connectivity are related with psychomotor speed and constructional praxis. Non-amnestic deficits are associated with frontal white matter in particular [33]. Also, callosal fibres seem crucial in the pathophysiology of cognitive impairment in VCI [29]. Of note, there is an ongoing study aimed at using a lesion-mapping approach that will hopefully elucidate the underlying basis of cognitive deficits in VCI [34] (Tab. 1).

Cognitive assessment

The lack of specific cognitive tools that are sensitive enough to detect subtle deficits make the assessment of cognitive impairment difficult. While much work has been done, e.g. in

Table 1. Pattern of most common focal neuropsychological deficits related to localization of infarcts

Localisation of infarct	Most common possible neuropsychological consequences
Left anterior cerebral artery	Executive dysfunction, aphasia
Right anterior cerebral artery	Executive dysfunction
Anterior communicating artery	Executive dysfunction; amnesia, aphasia
Left middle cerebral artery	Aphasia, apraxia, acalculia, verbal memory impairment
Right middle cerebral artery	Unilateral neglect, aprosody, spatial memory impairment
Posterior communicating artery	Memory impairment
Left posterior cerebral artery	Alexia, verbal memory impairment
Right posterior cerebral artery	Unilateral neglect, spatial memory impairment

AD [35], research into comparable protocols relating to VCI to detect subtle changes in cognitive performance is still scarce. Furthermore, culturally and linguistically relevant neuropsychological tests are lacking in populations with a higher incidence of stroke such as Asians, posing additional challenges to establish the prevalence of VCI in these populations.

One of the attempts to standardise the neuropsychological protocol for VaMCI was the introduction of harmonisation standards published by the National Institute of Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN). The authors proposed three neuropsychological test protocols of different lengths (60, 30, and 5 minute protocols) to be used in different settings which could evaluate the following cognitive domains: executive functions (using categorical and letter fluency and Digit Symbol-Coding subtest from Wechsler Adult Intelligence Scale-III (WAIS-III), visuospatial functions (Rey-Osterrieth Complex Figure), language (Boston Naming Test), memory (Hopkins Verbal Learning Test-Revised or California Verbal Learning Test-2) and neuropsychiatric and depressive symptoms (Neuropsychiatric Inventory, NPI) [36]. However, a VCI-subgroup-specific validation of those tests still remains to be carried out.

Following VASCOG criteria [11], there have been efforts to create summary scores that would enable the detection of cognitive impairment post stroke [37]. The drawback of the the proposed battery is the issue that selective but clinically important deficits (e.g. apraxia) might be missed by such summary scores.

Multilevel assessment of cognitive impairment in VCI

Since focal cognitive deficits, as well as overall cognitive decline, may be present in VCI, neuropsychological testing should consider both domain-specific neuropsychological disturbances (e.g. neglect) as well as global deterioration (e.g. dementia). As most patients with suspected VCI are of advanced age and suffer from fatigue, reduced attention capacity, behavioural alterations and other comorbid conditions, the testing needs to be relatively short or divided into two or more sessions. Moreover, significant sensory problems may exist, precluding the use of some cognitive tests with a special emphasis on these sensory abilities. In general, qualitative descriptions of cognitive symptoms are less favourable compared to operational definitions of cognitive impairment (e.g. performance 1 or 1.5 standard deviations below that of an appropriate comparison group) [5].

Hence, we suggest **a 2-level assessment procedure**, consisting of a primary screening (level A) which, at least in part, should also offer the possibility to be used at the bedside, plus a thorough evaluation (level B). This approach also takes into account the setting in which the neuropsychological assessment takes place (Tab. 2). Thus, while in the primary care setting (family physician or allied health professional) there is a need for time-efficient, global and sensitive cognitive measures, specific settings have different requirements: intensive care units (stroke units) follow a more tailored approach using measures that are able to identify specific deficits or core-syndromes (e.g. aphasia, apraxia), while memory clinic services are generally located more downstream in the diagnostic algorithm, thus allowing more in-depth protocols in order to postacutely describe the cognitive and behavioural profile for prognostic and rehabilitative purposes. When there are abnormal results in level A, patients should be referred to level B facilities, in order to i) submit them to a more specialised diagnostic setup once vascular pathology is suspected on the basis of level A findings, or ii) to optimise therapeutic efforts on the basis of an extended cognitive and behavioural assessment.

Neuropsychological tools should also offer the possibility of documenting changes over time in clinical status. As attention and executive deficits are regarded as core symptoms of VCI, particular measures should be used that are supposed to identify these deficits. However, since time-consuming and multiple-domain-involving tasks may obscure the underlying core deficit, neuropsychological testing should include straightforward as well as complex procedures. Moreover, in order to avoid ceiling, floor and practice effects, simple and short tasks with validated parallel versions, if available, should be administered.

Importantly, it must be considered that different tests have different sensitivities in different stages of a cognitive trajectory. Thus, while some tests (e.g. working memory-related tasks) may be useful in documenting incipient decline, they

Table 2. Extended neuropsychological assessment

	Stroke clinic	Memory clinic
Battery approach	Birmingham Cognitive Screen (BCoS); if no deficits evidenced – more extended memory and executive testing (see below)	Repeatable Battery for Assessment of Neuropsychological Status (RBANS); if no deficits evidenced – more extended executive testing (see below)
Tailored testing	Aimed at capturing focal syndromes as well as overall cognitive efficiency, so as to diagnose VCI or VaD	Aimed at specifying pattern of deficits to help with differential diagnosis
Language	Minimal assessment: naming, repetition, comprehension	Naming (e.g. BNT, SydBAT) comprehension (e.g. commands from BDAE)
Visuospatial functions	VOSP, line bisection, cancellation tasks	VOSP (Incomplete letters, Cube analysis)
Praxis	Praxis tasks with one hand (without motor impairment)	Interlocking fingers test
Episodic memory	If no aphasia and/or hearing impairment: CVLT/RAVLT/other verbal learning task	
	For individuals with particularly slowed information processing and/or impaired hearing: verbal learning lists presented visually (rate of presentation is adjusted to patient's slowing)	
	If visuospatial functions are mostly preserved: Location Learning Test BVMT-R	
Working memory	Months backwards; serial sevens, Digit Span, Spatial Span, TMT	
Executive functions	If confrontation naming is preserved: phonemic fluency tasks if visuospatial function is relatively preserved: Weigl block sorting task, picture sequencing task, Tower tests, Brixton Spatial Anticipation Test	

BDAE — Boston Diagnostic Aphasia Examination; BNT — Boston Naming Test; BVMT-R — Brief Visuospatial Memory Test-Revised; CVLT — California Verbal Learning Test; RAVLT — Rey Auditory Verbal Learning Task; SYDBAT — Sydney Language Battery; TMT — Trail Making Test; VCI — Vascular Cognitive Impairment; VaD — Vascular Dementia; VOSP — Visual Object and Space Perception Test

show a plateau (the floor effect) in more advanced stages and do not offer any specific diagnostic information. Hence for monitoring purposes it is mandatory to use tests which have more linear decelerating properties (e.g. semantic fluency and flexibility-related tasks). As information processing speed is usually compromised in VCI, in tasks assessing other aspects of cognition, the scoring should not be entirely time-dependent.

Finally, a neuropsychological diagnosis should consider both quantitative and qualitative data and take into account the apparent validity of the cognitive measures used. In some cases, one prominent deficit (e.g. executive deficit) may lead to low scores in almost all tasks. Conversely, some singular tests may require a set of different abilities and functions, thus qualifying them as global screening procedures and economising time for administration. Consequently, neuropsychological test results need to be interpreted in the context of behavioural observations, as a purely quantitative approach can lead to false conclusions.

Brief cognitive screening tests

The most commonly used instrument, MMSE, has only a low sensitivity in detecting MCI [38]. Using MMSE, only one study has provided information about conversion from MCI to VaD, presenting a sensitivity of 36%, and a specificity of 80% with incidence of VaD of 6.2% [39]. Despite the greater than MMSE sensitivity of MoCA to the milder forms of cognitive impairment with cerebrovascular disease [40], further longitudinal research is needed to verify its validity in detecting the progression of VCI [41]. A cut-off of 24/25 is suggested to detect post-stroke cognitive impairment [42]. However, MoCA is not sensitive enough to information processing deficits and visual memory impairment that are common in stroke survivors [43]. Also, it is much less sensitive to cognitive impairment following right-hemisphere strokes [44].

The short NINDS-CNS is a 5-minute protocol that can be used to identify high-risk groups for post-stroke dementia after acute ichaemic stroke. However, this test has been employed only in Korea [45] and China [46].

The cognitive screening instrument DemTect [47] is a short-screening test that has been extensively validated in different settings and languages. It was first published in 2000 in a German version, then in 2002 in a French, in 2004 in an English [48], and in 2016 in a Polish version [49]. In 2010, a parallel test, the DemTect B, was published [50] and in 2013, norms for people below 40 years and over 80 years were added [51]. In 2010, a modification of DemTect was developed by a Canadian workgroup to identify at-risk drivers [52]. DemTect consists of five subtests measuring short and long-term verbal memory, working memory, executive function, and number processing. The administration time is 8–10 minutes. Sensitivity and specificity of DemTect in studies with patients with dementia or MCI and healthy controls has been summarised in Kalbe et al. [53]. A condensed version which is suited for primary care settings is also available (RDST, rapid dementia screening test) [54].

Another screening instrument has recently been developed specifically for vascular MCI: the Brief Memory and Executive Test (BMET) covering executive functioning, processing speed, orientation, and memory [55]. MoCA and BMET are more sensitive in the detection of VCI than MMSE [56].

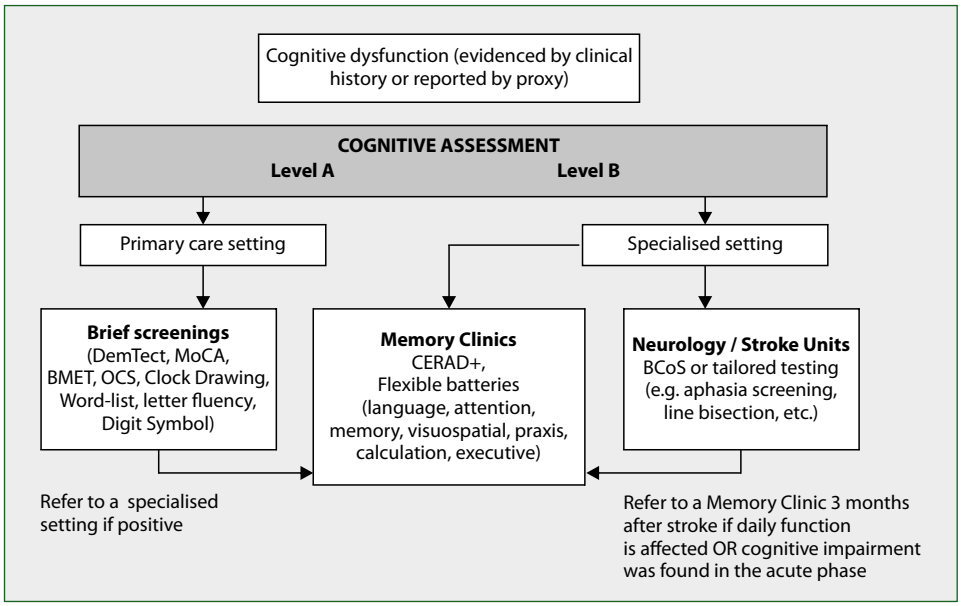

Figure 1. Cognitive assessment if vascular cognitive impairment is suspected.
BCoS — Birmingham Cognitive Screen; BMET — Brief Memory and Executive Test; CERAD+ — Consortium to Establish a Registry for Alzheimer's Disease; DemTect — Demenz Detection; MoCA — Montreal Cognitive Assessment; OCS — Oxford Cognitive Screen

The Oxford Cognitive Screen (OCS) incorporates tests for five cognitive domains: executive function, language, memory, number processing, and praxis [57], while the Cognitive Assessment for Stroke Patients (CASP) addresses language, visuospatial function, memory, praxis, and executive function [58]. CASP, unlike MMSE and MoCA, is applicable also in aphasic patients [59]. Both OCS and CASP address hemispatial neglect and apraxia. These are far more important in VaD than in neurodegenerative dementias. Although the diagnostic value of the Clock Drawing Test (CDT) depends on the scoring method, including quantitative and qualitative aspects [60], it is also regarded as a useful screening tool. Therefore it is recommended in a primary care setting since it probes executive as well as spatial functions. CDT together with a word learning trial, a letter fluency procedure and a naming task, is regarded as suited to a primary care setting to identify global cognitive deficits (Figure 1). Depending on the available assessment time and the patient's condition, these tasks can be either administered as single tasks or combined in a comprehensive short screening (e.g. MoCA, DemTect). Also, the Trail Making Test is sometimes recommended in the short screening context [61]. VASCOG experts suggest also other test combinations for shorter and longer screening, with semantic fluency - animal naming being the most commonly recommended measure [62].

Overall, cognitive screening tests, originally developed to screen for cognitive deficits in memory clinics, are not optimal measures to screen for cognitive impairment during the first month post stroke [63].

An alternative method for cognitive screening is the NeuroPsychological Examination (NPE). NPE is based on observation of the patient's behaviour during an examination. This semi-structured interview gives an opportunity to examine patients and acquire information about their daily functioning. However, its validity is strongly dependent on the clinician's experience [64] (Fig. 1).

Assessment of VCI at a stroke unit

Specialised units (e.g. stroke units/memory clinics) generally offer a far more sophisticated approach due to their extended resources in terms of time and personnel. Nonetheless, considering the patient's overall status when referred to these units, the examination procedure is presumed to be short and adaptable. As aphasia and unilateral neglect are quite common in stroke survivors, and most traditional neuropsychological assessments are not designed for people with language and/or hemispatial deficits, cognitive assessment at stroke units is particularly challenging e.g. when disentangling executive or memory deficits that might exist secondary to language or perceptual problems. Hence, some of the above-mentioned tests can be used or, alternatively, some intermediate batteries may turn out to be useful. As an example, the Birmingham Cognitive Screen (BCoS) offers the possibility to test cognition with minimal involvement of speech (e.g. orientation in time is tested in a multiple choice format). There is only a basic requirement of spatial attention (e.g. vertical alignment of stimuli), also probing for important cognitive aspects that are not included in most neuropsychological test batteries (praxis, calculation, spatial attention) [65]. Since this approach may contain

areas that could not adequately be assessed in some cases, a flexible battery of neuropsychological tests may be adopted.

Such a flexible battery involves the selection and administration of an array of tests that are based on the neuropsychologist's perception of the kind of brain damage that is allegedly present. Regarding the symptom variability, tests should probe the information processing speed, semantic and phonemic fluency, set-shifting, verbal learning (including free and cued short- and long-term recall), visuospatial functions and language abilities, as well as praxis and calculation.

Assessment of VCI at a memory clinic

Patients with suspected VCI are referred for neuropsychological assessment at a memory clinic usually in the context of a differential diagnosis with a primary neurodegenerative disease such as AD, dementia with Lewy bodies (DLB), or frontotemporal-dementia (FTD). Most memory clinics use a comprehensive and fixed battery of tests, all of which were standardised on the same group of people. This approach is called a fixed comprehensive standardised test battery.

The most commonly used test following this approach is the CERAD-NAB (Consortium to Establish a Registry for Alzheimer's Disease – Neuropsychological Assessment Battery). Though this battery was constructed to assess cognitive disturbances in suspected AD, and hence focuses primarily on cortical functions, a more recent extension of this battery was validated [66] by adding measures of speed and flexibility in order to improve diagnostic acuracy in VaD.

In case of a flexible approach, the cognitive assessment protocol should comprise at least one memory task with spontaneous delayed recall followed by either cued delayed recall or recognition to discriminate between storage (typical for AD and other pathologies involving the hippocampus) and retrieval deficit (typical for subcortical dementias). However, as neuropsychological profiles of VCI and DLB may overlap, neuropsychological assessment seems more promising in differentiating between VCI and AD than between VCI and DLB.

Mixed dementia (MD), i.e. the coexistence of Alzheimer's Disease (AD) and cerebrovascular disease (CVD), is a common dementia subtype [67]. It is increasingly recognised that patients with dementia and probable AD dementia commonly have mixed pathologies contributing to cognitive impairment. A study by Lei et al. [68] of 653 autopsied cases from two ongoing longitudinal cohort studies of individuals who were cognitively healthy at baseline (mean age = 79.1 years) analysing cognitive and neuropathological features, showed patients with AD pathology alone doubled the odds of developing dementia, and patients displaying mixed pathologies such as AD with macroinfarcts and/or Lewy body (LB) pathology markedly increased the odds, suggesting that AD pathology as well as vascular pathology are both associated with cognitive impairment.

Several studies have reported macroscopic and microscopic infarcts as well as amyloid angiopathy to be associated with a decline in perceptual speed and episodic memory loss [69]. In light of the striking overlap between AD and VaD contributing to cognitive impairment, it is difficult to establish a profile specific to degenerative or to vascular pathology. One of the few comparative studies, performed by Dong et al. [70], found the neuropsychological profile of patients with MD of mild-moderate severity to be characterised by a poorer global cognitive performance, as well as attention and visuoconstruction, than those with AD of mild-moderate severity. The TRACE–VCI study aimed to define the phenotype of VCI in a memory clinic setting by comparing different forms of vascular brain damage such as white matter hyperintensities, lacunar and non-lacunar infarcts and microbleed. However, the cognitive profiles of these vascular brain injuries were not signicantly different regardless of co-occurring AD [71].

Taken together, the neuropsychological differentiation between AD and MD still remains a diagnostic challenge. More comparative studies adopting comprehensive neuropsychological test batteries are needed to establish the cognitive profiles of mild-moderate MD, and compare it to the profiles of AD.

A more focused approach may also benefit from qualitative data on memory profile. Considering the performance pattern in verbal learning tasks, patients with AD profile reveal marked recency effect and less prominent primacy effect, while in MCI related to white matter hyperintensities either the opposite pattern or low serial position effects may be observed [72].

Behavioural and psychological symptoms in VCI/VaD

Behavioural and psychological symptoms of dementia (BPSD) affect almost all people at some point during the progression of VCI/VaD. In community-based studies, the prevalence of BPS ranges from 60% to 93% [73], whereas in memory units it is higher, ranging from 85% to 100% [74–76]. Besides the type of population (clinical, community or nursing-home settings), the definition of VCI/VaD and the instruments used to study the symptoms, differences in the prevalence and patterns of BPS between various studies may be due to other, often unconsidered, factors such as gender, age, education, use of medication and VCI/VaD severity.

In fact, except for depression, anxiety and euphoria, the frequency and diversity of BPS increases with the severity of cognitive impairment, leading to agitation, hallucinations, irritability, and disinhibition [75, 77]. There is still controversy regarding differences in BPS in different patient groups. While some authors have proposed that overall frequency and severity of BPS are higher in patients with VaD than in those with AD [77], some other groups have reported no significant difference [73, 74, 76, 78].

Although the literature dealing with BPSD in VCI/VaD is modest, some of these symptoms have been included in the criteria proposed for a diagnosis of VaD. The Hachinski Ischaemic Scale, a tool thought to be helpful in the differentiation of AD (cut-off score ≤ 4) from VaD (score ≥ 7), gives one

point for each of the following features: relative preservation of personality, depression and emotional incontinence [79]. Similarly, the NINDS-AIREN criteria include personality and mood changes, abulia, depression and emotional incontinence in the clinical features consistent with the diagnosis of probable VaD [10]. Most studies that have relied on VaD terminology have shown apathy to be the most common symptom (23–94%; [75]), followed by depression (21–85%; [73]), irritability (18–78%; [75, 76]), sleep disturbances (4–78%; [76, 78]) and agitation (21–77%; [75, 78]). Euphoria was the least common symptom (1.6–25%; [76]). A median number of three symptoms per patient has usually been reported [80].

When comparing VaD to AD, the most consistent findings are higher prevalence of delusions, aberrant motor behaviours [73, 74, 78], and hallucinations [74, 75] in AD. Other BPS such as agitation, anxiety, sleep disturbances and changes in appetite have been reported as being more common in AD in some studies, and in VaD in others [74, 76–78]. Compared to patients with DLB, patients with VaD had a lower score in hallucinations, agitation, irritability, anxiety and aberrant motor behaviours [74]. In contrast to FTD, disinhibition, aberrant motor behaviour and changes in appetite were less frequent in VaD [75].

These inconsistent results may be due to the fact that VCI/VaD is a heterogeneous entity with multiple causes (large vessel disease, small vessel disease, haemorrhagic stroke, strategically located lesions) being characterised by various clinical presentations. There appear to be differences in the individual BPS symptoms between sVaD and cVaD. Patients with sVaD had a higher severity of apathy [14, 80], aberrant motor behaviour and hallucinations [80] than patients with cVaD. In VaD, agitation and sleep disturbances are more common than in AD patients, and depression and aberrant motor behaviours appear more commonly in VaD than in mixed AD/VaD patients [81]. In contrast, symptoms of agitation [77, 80], sleep disturbances [77], and euphoria [80] were more severe in cVaD compared to sVaD.

In the most recent study, euphoria, apathy, irritability and agitation were more common in cVaD than in AD, while apathy and irritability were more frequent in sVaD than in AD. Psychotic symptoms and aberrant motor behaviour were more common in AD. A higher risk of euphoria, apathy, irritability and sleep disturbance was found in cVaD than in AD, and more apathy and irritability in sVaD than in AD. In contrast, AD subjects had a higher risk of delusions and hallucinations than patients with cVaD, as well as more aberrant motor behaviour than both cVaD and sVaD [82].

Recently there has been a tendency to conceptualise BPSD into "clusters" of symptoms that appear together: a) "affective" (including depression, anxiety); b) "apathy" (apathy, reduced appetite); c) "hyperactivity" (agitation, euphoria, irritability, disinhibition); and d) "psychosis" (hallucinations, delusions, abnormal motor behaviour (AMB) and sleep disturbances) [83]. Others have described three clusters: a) "mood" (anxiety, apathy, dysphoria); b) "psychosis" (irritability, delusions, hallucinations, agitation); and c) "frontal" (euphoria and disinhibition) in VaD [84].

Finally, it has been debated whether some BPSD in VaD are clinically distinct from those in other types of dementias. For example, compared to depression in AD, psychomotor symptoms such as loss of energy, and vegetative symptoms such as weight loss and loss of appetite, have been reported to be more prevalent in depression co-occurring within VaD [85]. One of the scales most commonly used to assess BPSD symptoms is the Neuropsychiatric Inventory (NPI), covering 12 areas of BPSD [86]. In addition, there are also available scales focused on the assessment of specific BPSD. Commonly used screening tests for depression in patients with suspected VCI include the Geriatric Depression Scale, the nine-item Patient Health Questionnaire, the Beck Depression Inventory, and the Centre for Epidemiologic Studies Depression Scale [87–89]. The Stroke Aphasic Depression Questionnaire or the Depression Intensity Scale Circles can be used to identify mood disturbance in VCI patients with aphasia [90, 91]. The Hamilton Depression Rating Scale and Hospital Anxiety and Depression Scale [HADS] are anxiety- and depression-specific case-finding instruments validated for use in stroke research [87, 92]. Also apathy can be identified by informant-rated specific scales such as the Apathy Evaluation Scale [93]. Of note, the presence of baseline VCI is predictive of apathy but not depression at 12-month follow-up [94].

The BPSD are associated with shorter life expectancy, excess disability, impaired quality of life for subjects and carers, high levels of caregiver distress, early institutionalisation, and increased direct cost of care. However, BPSD can be treated efficiently to improve the situation when correctly diagnosed [95].

The Neuropsychiatric Inventory Caregiver Distress Scale (NPI-D) is an instrument that provides a quantitative measure of the distress experienced by caregivers in relation to the individual symptom domains assessed by the NPI [96]. The Zarit Burden Interview (ZBI) is another validated and comprehensive instrument measuring caregiver burden [97]. Since the interview is a statement which the caregiver is asked to endorse, it is less appropriate to evaluate the burden associated with individual BPSD.

Prognosis and long-term management

Applying DSM–V criteria for major neurocognitive disorders (NCD) helps with defining a psychometric threshold for transition from MCI and small vessel disease (SVD) to major NCD. A longitudinal observation of 138 patients found that one–third of the multi–domain MCI patients with SVD progressed to major NCD after two years [98]. Interestingly, post-stroke cognitive impairment (PSCI) may be more closely related to the overall integrity of brain tissue that the volume of the new ischaemic lesion, as proved in a study in which 20% of patients developed PSCI during a 2-year observation [99].

Post-stroke VCI, unlike MCI in the context of neurodegenerative diseases (e.g. AD or Parkinson's Disease), or VCI with small vessel disease (VCI/SVD), may be quite stable for a couple of years and may thus hinder long-term prognosis about the conversion from VCI (at the mild cognitive impairment stage) to overt VaD. In VCI due to SVD, the conversion of VCI to VaD is usually heralded by the emergence of parkinsonian features. Thus, in a case of SVD or genetically caused vascular pathologies that are known to have a progressive course (e.g. cerebral autosomal dominant/recessive arteriopathy with subcortical infarcts and leukoencephalopathy — CADASIL / CARASIL, and mitochondrial encephalomyopathy lactic acidosis with stroke-like episodes — MELAS), regular neuropsychological follow-ups may be required to track the disease progression and formulate the recommendations for the patient and his/her family.

Such recommendations should include the preparations of powers of attorney for property and personal care, and the patient's ability to manage medication, which is particularly important in individuals with co-morbid insulin-dependent diabetes. Similarly, the impact of VCI on driving capacity needs to be considered.

Summary

Vascular cognitive impairment is an umbrella term comprising different forms and stages of cognitive decline, ranging from mild impairment to overt dementia. It is characterised most commonly by progressive accumulation of microvascular, or subcortical strokes, which results in progressive neurological dysfunction and cognitive as well as behavioural disturbances.

Dementia due to vascular damage is widely considered to be the second most common cause of dementia after AD. The diagnosis of vascular dementia is based on the presence of cerebrovascular disease of different origins, the identification of cognitive dysfunction, and a likely causal relationship between the two. Thus, once other causes of cognitive impairment have been excluded, the diagnosis can be established, if cognitive, as well as behavioural and motor symptoms characteristic of vascular origin and evidence of stroke or white matter lesions on neuroimaging arise. Given the various pathologies leading to VCI, it is no surprise that clinical symptoms can vary substantially in individual patients. Nonetheless, some cognitive features, executive dysfunctions, together with a reduced processing speed and failures of episodic memory are common, and make neuropsychological assessment mandatory.

Given that patients with vascular deficits can appear in different clinical settings, we suggest a two-level assessment procedure consisting of a primary short screening (level A) and an in-depth evaluation (level B). This proposal is in agreement with a recent UK consensus on VCI which advocates the same approach, stating that a single mandated outcome assessment would not be suitable for a complex construct such as VCI [100].

Behavioural disturbances are also common in VCI and may even dominate the clinical picture at some stages, leading to a significant caregiver burden. Compared to AD, there is still a great need for prospective, cross-sectional and longitudinal studies on BPS in VCI. Although there are no consensus criteria about the methodology for screening and investigating BPS in VCI, it is strongly recommended to use standardised protocols to assess BPSD (NPI) as well as caregiver burden (ZBI).

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