NEW HORIZONS

New horizons in cognitive and functional impairment as a consequence of cerebral small vessel disease

LISANNE TAP[1], MEIKE W. VERNOOIJ[2], FRANK WOLTERS[3], ESTHER VAN DEN BERG[4], FRANCESCO U.S. MATTACE-RASO[1]

[1]Department of Internal Medicine, Section of Geriatric Medicine and Alzheimer Center Erasmus MC, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[2]Department of Radiology and Nuclear Medicine and Alzheimer Center Erasmus MC, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[3]Department of Epidemiology and Alzheimer Center Erasmus MC, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[4]Department of Neurology and Alzheimer Center Erasmus MC, Erasmus MC University Medical Center, Rotterdam, The Netherlands

Address correspondence to: Francesco U.S. Mattace-Raso, Section Geriatric Medicine, Department of Internal Medicine Erasmus MC, University Medical Center Rotterdam, Room Rg-525, PO BOX 2040, Rotterdam 3000 CA, The Netherlands. Tel: (+31)10703 5979; Fax: (+31)10703 47 68; Email f.mattaceraso@erasmusmc.nl

Abstract

Cerebral small vessel disease (cSVD) is a frequent finding in imaging of the brain in older adults, especially in the concomitance of cardiovascular disease risk factors. Despite the well-established link between cSVD and (vascular) cognitive impairment (VCI), it remains uncertain how and when these vascular alterations lead to cognitive decline. The extent of acknowledged markers of cSVD is at best modestly associated with the severity of clinical symptoms, but technological advances increasingly allow to identify and quantify the extent and perhaps also the functional impact of cSVD more accurately. This will facilitate a more accurate diagnosis of VCI, against the backdrop of concomitant other neurodegenerative pathology, and help to identify persons with the greatest risk of cognitive and functional deterioration. In this study, we discuss how better assessment of cSVD using refined neuropsychological and comprehensive geriatric assessment as well as modern image analysis techniques may improve diagnosis and possibly the prognosis of VCI. Finally, we discuss new avenues in the treatment of cSVD and outline how these contemporary insights into cSVD can contribute to optimise screening and treatment strategies in older adults with cognitive impairment and multimorbidity.

Key Points

- Currently used tools to quantify the consequences of cerebral small vessel disease (cSVD) still seem insufficient to capture the complete clinical spectrum of vascular cognitive impairment (VCI).
- Advances in imaging may improve specificity of cSVD features for underlying aetiology as well as functional consequences.
- Assessment of cognitive impairment in cSVD should include novel sensitive and qualitative measures.
- The contribution of vascular causes in cognitive deficits should be interpreted in context of imaging and functional markers.
- A multidimensional assessment is needed to plan interventions in patients with VCI.

Introduction

Cerebral small vessel disease (cSVD) is an umbrella term for alterations in the function or structure of the arteriolar, capillary and venular vessels [1]. cSVD frequently occurs in the brain of older persons and can be indirectly visualised on brain imaging through markers such as cerebral white matter hyperintensities (WMH), microbleeds and lacunar infarcts [2]. These vascular alterations are mostly due to a cumulative exposure to detrimental internal and external influences [3], such as genetic profiles and cardiovascular risk factors. Consequently, cSVD is highly prevalent with ageing, affecting almost all older adults above the age of 90 years. The clinical consequences, however, vary greatly between individuals. When cSVD leads to cognitive impairment, it is labelled part of the spectrum of vascular cognitive impairment (VCI), which ranges in severity from mild cognitive impairment to dementia, and can reflect pure VCI or a mixed phenotype with for example Alzheimer's disease (AD) or Lewy body pathology [4]. In others, cSVD may lead to mood disorders, stroke or gait disturbances and consequent functional decline [5–7]. Yet, a large number of individuals with substantial cSVD on brain imaging does not experience symptoms at all [8]. It remains undetermined how and in which stage or form these vascular alterations lead to cognitive and functional deterioration in some persons and not in others, since those with more extensively affected brains are not necessarily the ones with the most clinical symptoms. In this review, we aim to describe the latest developments and new horizons with respect to the diagnosis of cSVD and its implications for cognitive and functional impairment. How can we assess cSVD accurately? How do we identify the contribution of cSVD to cognitive impairment in individual patients? And how do we determine which patients with cSVD have the greatest risk of further cognitive and functional deterioration? In order to discuss these points, we will focus on new horizons in those tools that are already available and used in a standard clinical setting: neuroimaging techniques, neuropsychological assessment and subsequently the potential functional impact of cSVD in older adults with cognitive impairment.

Neuroimaging aspects

Brain imaging with either computed tomography (CT) or—preferably—magnetic resonance imaging (MRI) is the cornerstone of the identification and assessment of the severity of cSVD. Whereas established imaging markers on conventional MRI such as WMH, lacunar infarcts and microbleeds are well incorporated in everyday clinical radiological assessment, there is at present a gap in linking the extent of vascular brain injury seen on images to cognitive impairment. [8, 9] Whilst standardised criteria, such as the Standards for Reporting Vascular Changes on Neuroimaging 1 (STRIVE-1) [10] and the more recently introduced STRIVE-2 [11], have helped to determine the extent and clinical consequences of cSVD for research use, such criteria are not yet

available for more novel imaging markers or need substantial harmonisation efforts [12]. Translating brain imaging into clinical profiles in cSVD could be improved by several developments in image acquisition, interpretation or processing, further described below.

Direct and specific measures of underlying pathology

Neuroimaging covers a wide array of markers for vascular brain injury, ranging from structural abnormalities (e.g. lacunar infarcts and microbleeds) to functional components of the neurovascular unit (e.g. cerebrovascular reactivity, blood brain barrier integrity) (Table 1). Whilst these are all considered markers of vascular brain injury, their aetiology is heterogeneous, with various potential underlying causes even within a single marker. Well acknowledged, mostly structural markers like lacunar infarcts and WMH play an important role in the recognition and etiological diagnosis of VCI, but still are indirect markers of vascular injury, as spatial resolution of routine imaging techniques is insufficient to capture the smaller arterioles and capillaries *in vivo*. Functional changes in the cerebral small vasculature, on the other hand, thus far primarily serve to improve our understanding of VCI pathophysiology in a research setting. Translation of the latter to clinical practice is hindered by poor specificity of the marker, lack of validation studies, technological requirements, or challenges in the transportability and interpretation of results. Examples include WMH (i.e. nonspecific) [13], diffusion tensor imaging (lack of validation and transportability) [14] and blood brain barrier integrity (validation as well as technological challenges and contrast requirement) [15]. Better understanding of the pathology reflected by (different patterns of) imaging abnormalities and development of more specific markers is needed for more fine-grained diagnosis, both differentiating VCI from other causes of cognitive impairment, and pinpointing the specific aetiology within the realm of VCI. With respect to more specific markers, exciting results were derived from ultrahigh field MRI studies that demonstrated the ability, taking advantage of inherent increased spatial and temporal resolution, to directly image perforating arteries and flow velocity and pulsatility within them [16]. Though such measures are a far leap from clinical practice, they hold promise for improving insight into cSVD pathogenesis and as potential endpoints in clinical trials.

cSVD as manifestation of global disease

Though many of the currently used imaging markers seemingly represent very focal brain damage (e.g. WMH, lacunar infarcts, microbleeds), there is increasing insight into the fact that cSVD is not a focal issue, but has diffuse effects across the brain. Diffusion imaging studies of the white matter demonstrate that there is a global decrease in integrity of microstructural integrity in the 'normal-appearing' white matter outside regions of WMH, which also impact cognitive functioning [17]. Furthermore, the classically recognised

Table 1. Overview on how to measure, define and use imaging markers of cSVD

Imaging marker	Modality (sequence)	Definition	Current use
Cortical infarcts macroinfarcts	MRI or CT	Tissue loss of presumed ischemic origin involving cortical grey matter, with/without surrounding gliosis	Clinical + Research
Cortical infarcts microinfarcts [11, 34]	MRI ($\geq$3 Tesla; DWI/T1/T2)	small lesions of cortical tissue loss in accordance with visual rating criteria, with upper limit of 4 mm	Research
WMH [13]	MRI (T2/FLAIR) or CT	Volumetric or semi-quantitative rating scales (Fazekas, ARWMC)	Clinical + Research
Recent small subcortical infarcts and lacune (of presumed vascular origine) [11]	MRI (or CT)	STRIVE-2 criteria	Clinical + Research
Perivascular spaces [35, 36]	MRI	Visual rating; automated detection algorithms in development	Research
Cerebral microbleeds [37, 38]	MRI (T2/SWI)	Visual rating (MARS, BOMBS rating scales) or automated computer-aided detection	Clinical + Research
Microstructural white matter damage [14]	MRI (DWI, MTR)	Volume scores using automated computer-aided detection	Research
Blood flow and perfusion [39]	MRI (PC, ASL, DSC/DCE), CT-perfusion	The rate of delivery of arterial blood to the capillary bed	Clinical (in stroke or hemodynamic impairment) + Research
Blood brain barrier integrity [15]	MRI (DCE/DSC/DWI)	Measure and informativeness differ depending on the applied method	Research
Cerebral vasoreactivity [40]	MRI (ASL, BOLD fMRI) or transcranial Doppler	*The ability of the blood vessels to dilate in order to match tissue blood supply to increased* demand; usually measured through a challenge with acetazolamide, breath holding, or CO_2	Clinical (in context of stroke and hemodynamics) + Research
Pulsatility [41]	MRI (CE or 4D-PC) or transcranial Doppler	Difference between maximum and minimum flow divided by the mean flow across regions of interest	Research

Abbreviations: WMH, white matter hyperintensities; (f)MRI, (functional) magnetic resonance imaging; CT, computed tomography; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; SWI, susceptibility-weighted imaging; MTR, magnetisation transfer ratio; PC, phase contrast; ASL, arterial spin labelling; DSC, dynamic susceptibility contrast; (D)CE, (dynamic) contrast enhanced; BOLD, blood oxygenation level dependent; 4D, four-dimensional; ARWMC, age-related white matter changes; MARS, microbleed anatomical rating scale; BOMBS, brain observer microbleed scale; CO_2, carbon dioxide.

focal lesions are linked to structural and functional alterations in remote brain regions, through network connections [18]. Taken together, it is often remarked that conventional imaging markers only show the 'tip of the iceberg' of total SVD-related damage [19]. Consequently, VCI is not fully explained by burden of visible focal lesions, but also through more global measures. This global aspect of cSVD should thus be taken into account both in research as well as (ultimately) in clinical assessment [20].

Location-specific information of focal cSVD lesions

Despite the inherent global nature of underlying cSVD pathology, the focal lesions visible on conventional imaging may harbour more relevant information with respect to cognition than is currently being exploited. Explaining cognitive impairment through brain imaging findings may be improved by taking lesion location into account [21]. Recent studies demonstrate that WMH burden in specific tracts (such as the anterior thalamic radiation), are more relevant in explaining cognitive variation than overall WMH burden. Furthermore, focal lesions may indicate a locally more active vasculopathy, as evidenced for example by reports of macrohemorrhage or focal inflammation being related to

local clustering of microbleeds or WMH [22, 23]. Similarly, location of cerebral microbleeds may points towards their underlying aetiology [9]. These observations suggest that in the future, clinical assessment of cSVD should move away from only assessing global burden to more location-specific implications.

Defining what is 'normal' to recognise 'abnormal'

To explain how cSVD causes cognitive impairment in individual patients, understanding what is 'normal' in brain ageing is of utmost importance, as common imaging markers in cSVD are also frequently seen in general ageing populations [24]. For example, the presence of cerebral infarcts unequivocally indicate vascular pathology, whereas microstructural changes on diffusion tensor imaging likely have a broader 'normal' range that may or may not imply pathological abnormality. Even for WMH in an older population with cognitive impairment, many individuals may have some degree of WMH that is not necessarily related to their cognition. No reference data are currently available to define 'normality', for example in WMH burden per age and sex-categories. Being able to reference individual burden of cSVD in a clinical setting against normative reference

data could help to distinguish the normal ageing brain from pathological patterns, similar to brain atrophy measures.

Improving prognostic insight through better assessment of total burden of cSVD

The precise utility of neuroimaging markers of cSVD in clinical setting depends on the purpose. Prognosis may be served by aggregate measures of vascular brain injury to obtain a more robust predictive measure that captures the vascular component in its entirety [25]. Such aggregate measures may be derived through simple (weighted) sum scores of markers (for which the proposed STRIVE-2 term would be summary SVD score [11, 26]), but could also result from more advanced statistical techniques like dimensionality reduction (principal component analysis) or machine-learning (pattern recognition) [27]. In research setting, summary SVD scores have been demonstrated to relate to clinical outcomes, but as of yet with insufficient magnitude and validation to warrant their use in routine clinical practice [28, 29]. Similarly, machine-learning techniques are generally able to identify detrimental patterns of (vascular) brain injury on imaging, but their predictive value rarely exceeds that of acknowledged, individual markers and is often hampered by methodological drawbacks [30].

In contrast to prognostic purposes, aetiological diagnosis and subsequent (personalised) treatment are best served by specific (and therefore individual) markers of underlying pathology. The development of effective treatments against VCI may well depend on the ability of neuroimaging to detect the specific target pathologies, such as cerebral amyloid angiopathy. This applies to treatment efficacy as well as harm. With the availability of novel monoclonal antibodies for treatment of AD, identifying through neuroimaging subjects who are at risk of side effects (e.g. amyloid-related imaging abnormalities) due to concomitant vascular pathology will become increasingly important [31, 32]. In older patients with cognitive impairment, in whom vascular pathology commonly coincides with other neuropathology, measures of vascular injury might help to select patients in whom the potential benefit of targeted treatment outweighs its risk of harm.

With respect to the current role of imaging within the diagnostic work-up of cognitive complaints, structural imaging serves primarily to identify potential underlying causes for cognitive decline when clinical uncertainty exists about the neurodegenerative nature of complaints. In particular cases, there may be need for imaging to inform a nosological diagnosis. Whilst such decisions are informed by the needs of patients and physicians, the clinical implications of potential findings, either for prognosis or treatment, should be leading in the use of any diagnostic tool. Thus, should we offer neuroimaging to all patients presenting with cognitive complaints to assess cSVD? At this stage, the answer would be a clear 'no'. As endorsed in most clinical guidelines [33], this may well change in the face of aforementioned disease modifying therapies and validation of novel imaging tools whilst current prognostic value and (lack of) targeted treatment often limit the implications of brain imaging.

The neuropsychological fingerprint

Neuropsychological testing is key to defining the precise place on this severity spectrum of VCI. In both research and clinical settings brief cognitive screening instruments such as the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) are often administered [42, 43]. Although screening instruments are quick and easy to use, these instruments have been developed to screen for cognitive deficits due to AD and focus on the dementia stage. The MMSE does not include items measuring processing speed or executive functioning, making it insensitive to recognise the consequences of cSVD. The MoCA has a better sensitivity in detecting cognitive impairment, in particular for VCI, but poorer specificity resulting in more false positives [44]. These cognitive screening instruments thus fail to capture the nature and extent of VCI.

Assessment of subtle cognitive impairment

The 'classic' profile of VCI is characterised by slowed information processing speed, impaired working memory capacity and executive deficits in the absence of specific 'cortical' impairment such as aphasia, amnesia or agnosia. This classic view is an oversimplification as all cognitive functions can be (modestly) impaired in cSVD with similar effect sizes across cognitive domains [45, 46]. The cognitive profile may not reflect deficits in specific cognitive domains per se, but rather a more global impairment that results from disconnection of cortico-limbic connections affected by vascular brain damage. The cognitive profile is also (at least in part) dependent on the nature and location of the vascular injury.

Subtle cognitive impairments may be present already in mild cSVD. In the general population vascular risk factors such as type 2 diabetes mellitus, hypertension, dyslipidaemia and obesity are associated with modest cognitive impairment (effect size Cohen's d ∼0.3) [47]. Similarly, the presence of WMH in the general population is associated with a relatively small but consistent negative effect of cognitive functioning across different cognitive domains (memory, processing speed, executive functioning, perception/construction) [46]. In addition, cognitive disturbances following lacunar infarction reflect a general decrease in performance rather than focal cognitive impairments in specific cognitive domains. This subtle decreased performance can be characterised as a reduction in mental capacity that is particularly evident in strenuous, more demanding cognitive tasks [48].

The cognitive sequelae of new (imaging) markers of cSVD—such as microstructural integrity of normal appearing white matter—are scarcely investigated [49, 50] and traditional quantitative neuropsychological tests are unlikely to measure these potentially subtle cognitive impairments. Neuropsychological assessment should therefore consider

both quantitative and qualitative information on cognitive functioning, including the way a particular cognitive performance is accomplished. For example, a prominent impairment in executive functions may lead to decreased performance in most other cognitive tests. Conversely, a single test performance may require a broader set of cognitive abilities. Qualitative and dynamic measures of cognitive impairment may be promising [51, 52], whereas application and validation of such measures in populations with cSVD is currently lacking.

Different harmonisation protocols for cognitive testing in cSVD have been proposed [53]. Detailed cognitive screening procedures, such as the Brief Memory and Executive Test and the Oxford Cognitive Screen [54, 55], appear valid in post stroke populations, however, the validity and reliability in patients with cSVD remain to be evaluated. A tailored approach to cognitive assessment in cSVD should also offer the possibility of documenting clinical changes over time. Testing procedures may not be equally valid in different stages and ceiling, floor and practice effects should be avoided. For example, working memory procedures tend to show floor effect in more advanced stages of cognitive impairment. Cognitive tests that are able to document incipient decline are therefore preferred.

Vascular contribution to cognitive impairment of mixed aetiology

In a large percentage of patients, cSVD is accompanied by other types of neurodegenerative pathology. The co-occurrence of pathology increases with age. At the time of death, nearly 80% of community-dwelling individuals have multiple types of brain pathology, at least one of which is of a vascular nature [56]. Mixed pathologies are the rule rather than an exception in older persons with cognitive impairment. Consequently, potentially distinguishable cognitive phenotypes merge into a more generalised cognitive deficit in older patients. The VCI concept allows for concomitant contributions of other pathologies, such as AD, to the phenotype of individual patients with cSVD.

cSVD and degenerative pathologies not only co-occur; the presence of cSVD modulates the nature and severity of cognitive impairment in AD [57, 58]. The presence of WMH is associated with cognitive impairment in persons with mild cognitive impairment or (Alzheimer's) dementia [59]. It is therefore not surprising that the ability of neuropsychological assessment to reliably differentiate between underlying Alzheimer type and/or vascular brain pathology is overestimated. A cognitive profile with 'cortical' characteristics (amnesia, aphasia, agnosia) increases the chance of a clinical diagnosis of AD, but the additional contribution of vascular brain damage may be overlooked.

Despite the presence of multiple pathologies in individual persons the custom in memory clinics is to assign a 'main' (monocausal) etiological diagnosis. In older persons with cognitive impairment due to both Alzheimer pathology and cSVD this may lead to withholding of (either symptomatic or disease modifying) treatment against either cause. Tailored, optimal disease management can only be reached when markers of cSVD are evaluated in the context of other neuropathology. We should thus aim to specify and measure the *relative* contribution of vascular and other neuropathological causes of cognitive impairment in individual persons. This requires detailed recording of cognitive deficits in close accordance with both imaging and functional markers of cSVD.

Functional aspects related to cSVD

Functional decline in patients with cSVD goes well beyond cognitive impairment alone, and may involve decline in mobility and dexterity contributing to impairment in activities of daily living. The performance of daily activity has a specific level of complexity and requires specific cognitive skills. The presence of cSVD plays a role in determining both cognitive and functional outcomes in older individuals and cSVD is a major determinant of mobility problems in older adults [7, 60]. The LADIS study showed that around a quarter of patients with severe cSVD decline from functional autonomy to disability after only 1 year follow-up [61]. In the Rotterdam study, it was shown that motoric cognitive risk syndrome, defined as subjective cognitive complaints and slow gait speed, was associated with imaging markers as WMH and risk of dementia [62]. These results highlight the relevance of assessment of motor function in early risk stratification for VCI.

Several mechanisms can explain associations between cSVD and functional disability. Gait and balance disorders are the second most common problem in patients with cSVD leading to falls, decreased functional independency and higher risk of admission to nursing homes or mortality [63, 64]. Gait and balance are considered to be regulated by multisystem interactions, suggesting that these disorders can be caused by different pathological mechanisms, related in the brain to executive functions such as attention, visuospatial and motor processes [65]. cSVD, by damaging fibre bundles and loops, can cause impaired visual, cognitive, sensory and motor functions [66]. The cerebral regions that are most often affected by cSVD and responsible for these manifestations are the frontal and the temporal lobe and the basal ganglia. Moreover, the decline in cognitive functions, especially in ageing persons with a diminished muscle mass and decreased control ability can be linked to gait and balance disorders [67]. Conversely, cSVD can disrupt motor pathways such as the cortex-striatum-globus pallidus-thalamic-cortical circuit, increasing the risk of gait disorders [68]. The severity of WMH in the deep frontal lobe and the periventricular WMH (PWMH) significantly impairs balance function in the older population, which supported the hypothesis that the disruption of motor circuits in the subfrontal cortex caused balance disorders [69]. Also, it has been reported that gait and balance disorders in patients with VCI were mainly characterised by
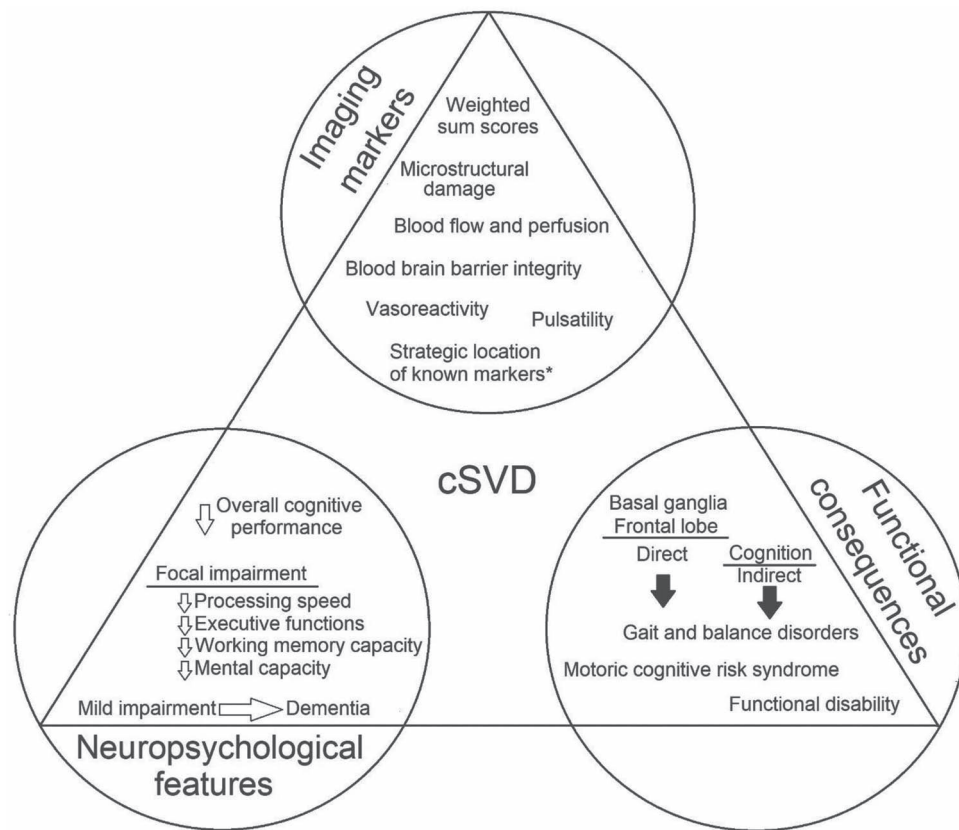
Figure 1. The triangle of vascular cognitive impairment due to cSVD.

reduced arm swing, reduced step length and broad base gait, which were possibly caused by PWMH volume and white matter integrity but not with other radiological markers of cSVD [70]. Lacunar infarcts are usually covert, and can be found in 20–50% of older adults [71], but can also affect gait and balance function through direct damage to motor pathways, such as the frontal lobe and basal ganglia and, indirectly, by influencing cognition; when located in the frontal lobe and thalamus it can cause low gait speed as reported in population-based studies [72]. Moreover, the presence of both WMH and lacunar infarcts can contribute exponentially to the impairment of gait and postural stability in aged patients [73].

In addition, a substantial burden of all-cause dementia and depression is attributable to cSVD [6]. Apathy and fatigue are common after stroke and there is increasing evidence that these manifestations are also frequently found in individuals with cSVD [74, 75]. Also delirium is associated with severity of cSVD suggesting that individuals with underlying small vessel disease have more frail brains, in which areas of vascular dysfunction can be more susceptible to acute impairment following systemic inflammatory insults [76]. The awareness that these manifestations are common in patients with cSVD could prompt clinicians to seek out and monitor these symptoms in individuals with cardiovascular risk factors and therefore at risk for cSVD. Eventually, in

older adults, a higher burden of cSVD has been associated with frailty and progression of frailty [77].

Whilst neurodegenerative diseases are chronic and currently incurable, the length of time between diagnosis and complete functional dependency can be many years. Therefore, the assessment of functional status in multimorbid, frail older patients with cSVD is of paramount importance and needs to become an essential component of the comprehensive assessment. Different scales based on interviews with the patient or the caregiver of the patient can be used to objectively measure decline in everyday functional skills [78], whereas physical performance and mobility skills can be assessed by the short physical performance battery [79].

Considerations for treatment

As suggested by the recent European Stroke Organisation Guideline, only a small number of studies investigated cardiovascular risk management in patients with covert cSVD [80]. Blood pressure and glucose levels in patients with hypertension and diabetes respectively should carefully be controlled according to current guidelines. The use of statin is not likely to cause much harm and may do some good, whereas patients with cSVD should not take drugs like aspirin or clopidogrel, unless there is a history of a previous heart attack or stroke. The evidence that treating

hyperglycemia and hypercholesterolemia reduces the risk of VCI and dementia in general is relatively low [81, 82]. The standard or intensive treatment of hypertension has a modest effect on delaying cognitive decline [83], which may depend in part on drug class [84]. However, most studies were not primarily designed to investigate cognitive outcomes. Therefore, randomised controlled trials investigating the effect of cardiovascular risk management on cognitive decline are needed. Eventually, as suggested by the FINGER trial, a multi-domain intervention could reduce the incidence of cardiovascular events in order to prevent cognitive impairment and disability in ageing populations [85]. Given the multifactorial nature of VCI, a comprehensive assessment is mandatory for planning multicomponent interventions including the treatment of comorbidities, the monitoring of cognitive and functional decline to provide support in order to maximise individual independence. Figure 1 shows an overview of discussed insights on VCI as consequence of cSVD.

Finally, improvements in diagnosis of cSVD and VCI are equally needed in the context of other neurodegenerative diseases. With the recent approval by the Food and Drugs Administration of monoclonal antibodies against amyloid-beta for the treatment of AD, it has become ever more necessary to quantify the contribution of cSVD to cognitive impairment in patients presenting with cognitive impairment in the presence of AD. Neuropsychological assessment in combination with advanced (use of) imaging markers, and other novel types of (fluid) biomarkers may well be our crucial aids in the treatment selection in such clinical trials as well as routine clinical practice.

Declaration of Conflicts of Interest: None.

References

1. Benveniste H, Nedergaard M. Cerebral small vessel disease: a glymphopathy? Curr Opin Neurobiol 2022; 72: 15–21.
2. Li Q, Yang Y, Reis C *et al.* Cerebral small vessel disease. Cell Transplant 2018; 27: 1711–22.
3. Cannistraro RJ, Badi M, Eidelman BH, Dickson DW, Middlebrooks EH, Meschia JF. CNS small vessel disease. Neurol Genetics 2019; 92: 1146–56.
4. Gorelick PB, Scuteri A, Black SE *et al.* Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011; 42: 2672–713.
5. Bos D, Wolters FJ, Darweesh SKL *et al.* Cerebral small vessel disease and the risk of dementia: a systematic review and meta-analysis of population-based evidence. Alzheimers Dement 2018; 14: 1482–92.
6. van Sloten TT, Sigurdsson S, van Buchem MA *et al.* Cerebral small vessel disease and association with higher incidence of depressive symptoms in a general elderly population: the AGES-Reykjavik study. Am J Psychiatry 2015; 172: 570–8.
7. Jokinen H, Koikkalainen J, Laakso HM *et al.* Global burden of small vessel disease–related brain changes on MRI predicts cognitive and functional decline. Stroke 2020; 51: 170–8.
8. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. Lancet Neurol 2013; 12: 483–97.
9. Greenberg SM, Vernooij MW, Cordonnier C *et al.* Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol 2009; 8: 165–74.
10. Wardlaw JM, Smith EE, Biessels GJ *et al.* Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013; 12: 822–38.
11. Duering M, Biessels GJ, Brodtmann A *et al.* Neuroimaging standards for research into small vessel disease-advances since 2013. Lancet Neurol 2023; 22: 602–18.
12. Smith EE, Biessels GJ, De Guio F *et al.* Harmonizing brain magnetic resonance imaging methods for vascular contributions to neurodegeneration. Alzheimers Dement (Amst) 2019; 11: 191–204.
13. Wahlund LO, Barkhof F, Fazekas F *et al.* A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001; 32: 1318–22.
14. de Groot M, Ikram MA, Akoudad S *et al.* Tract-specific white matter degeneration in aging: the Rotterdam study. Alzheimers Dement 2015; 11: 321–30.
15. Elschot EP, Backes WH, Postma AA *et al.* A comprehensive view on MRI techniques for imaging blood-brain barrier integrity. Invest Radiol 2021; 56: 10–9.
16. van den Brink H, Doubal FN, Duering M. Advanced MRI in cerebral small vessel disease. Int J Stroke 2023; 18: 28–35.
17. Vernooij MW, Ikram MA, Vrooman HA *et al.* White matter microstructural integrity and cognitive function in a general elderly population. Arch Gen Psychiatry 2009; 66: 545–53.
18. Tuladhar AM, Lawrence A, Norris DG, Barrick TR, Markus HS, de Leeuw FE. Disruption of rich club organisation in cerebral small vessel disease. Hum Brain Mapp 2017; 38: 1751–66.
19. Ter Telgte A, van Leijsen EMC, Wiegertjes K *et al.* Cerebral small vessel disease: from a focal to a global perspective. Nat Rev Neurol 2018; 14: 387–98.
20. Blair GW, Hernandez MV, Thrippleton MJ, Doubal FN, Wardlaw JM. Advanced neuroimaging of cerebral small vessel disease. Curr Treat Options Cardiovasc Med 2017; 19: 56. https://doi.org/10.1007/s11936-017-0555-1.
21. Coenen M, Kuijf HJ, Huenges Wajer IMC *et al.* Strategic white matter hyperintensity locations for cognitive impairment: a multicenter lesion-symptom mapping study in 3525 memory clinic patients. Alzheimers Dement 2022; 19: 2420–32.
22. Akoudad S, Portegies ML, Koudstaal PJ *et al.* Cerebral microbleeds are associated with an increased risk of stroke: the Rotterdam study. Circulation 2015; 132: 509–16.

23. Auriel E, Charidimou A, Gurol ME et al. Validation of Clinicoradiological criteria for the diagnosis of cerebral amyloid Angiopathy-related inflammation. JAMA Neurol 2016; 73: 197–202.

24. Vinke EJ, de Groot M, Venkatraghavan V et al. Trajectories of imaging markers in brain aging: the Rotterdam study. Neurobiol Aging 2018; 71: 32–40.

25. Low A, Prats-Sedano MA, McKiernan E et al. Modifiable and non-modifiable risk factors of dementia on midlife cerebral small vessel disease in cognitively healthy middle-aged adults: the PREVENT-dementia study. Alzheimers Res Ther 2022; 14: 154. https://doi.org/10.1186/s13195-022-01095-4.

26. Staals J, Makin SD, Doubal FN, Dennis MS, Wardlaw JM. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. Neurology 2014; 83: 1228–34.

27. Makkinejad N, Evia AM, Tamhane AA et al. ARTS: a novel in-vivo classifier of arteriolosclerosis for the older adult brain. Neuroimage Clin 2021; 31: 102768. https://doi.org/10.1016/j.nicl.2021.102768.

28. Yilmaz P, Ikram MK, Niessen WJ, Ikram MA, Vernooij MW. Practical small vessel disease score relates to stroke, dementia, and death. Stroke 2018; 49: 2857–65.

29. Suzuyama K, Yakushiji Y, Ogata A et al. Total small vessel disease score and cerebro-cardiovascular events in healthy adults: the Kashima scan study. Int J Stroke 2020; 15: 973–9.

30. Volovici V, Syn NL, Ercole A, Zhao JJ, Liu N. Steps to avoid overuse and misuse of machine learning in clinical research. Nat Med 2022; 28: 1996–9.

31. Reish NJ, Jamshidi P, Stamm B et al. Multiple cerebral Hemorrhages in a patient receiving Lecanemab and treated with t-PA for stroke. N Engl J Med 2023; 388: 478–9.

32. van Dyck CH, Swanson CJ, Aisen P et al. Lecanemab in early Alzheimer's disease. N Engl J Med 2023; 388: 9–21.

33. National Institute for Health and Care Excellence "Dementia: Assessment, Management and Support for People Living with Dementia and their Carers." 2018 ISBN: 978-1-4731-2978-8 [updated Jun. Available from: https://www.nice.org.uk/guidance/ng97/chapter/recommendations#diagnosis.

34. van Veluw SJ, Shih AY, Smith EE et al. Detection, risk factors, and functional consequences of cerebral microinfarcts. Lancet Neurol 2017; 16: 730–40.

35. Potter GM, Doubal FN, Jackson CA et al. Enlarged perivascular spaces and cerebral small vessel disease. Int J Stroke 2015; 10: 376–81.

36. Moses J, Sinclair B, Law M, O'Brien TJ, Vivash L. Automated methods for detecting and quantitation of enlarged perivascular spaces on MRI. J Magn Reson Imaging 2023; 57: 11–24.

37. Gregoire SM, Chaudhary UJ, Brown MM et al. The microbleed anatomical rating scale (MARS): reliability of a tool to map brain microbleeds. Neurology 2009; 73: 1759–66.

38. Cordonnier C, Potter GM, Jackson CA et al. Improving interrater agreement about brain microbleeds: development of the brain observer MicroBleed scale (BOMBS). Stroke 2009; 40: 94–9.

39. Jahng GH, Li KL, Ostergaard L, Calamante F. Perfusion magnetic resonance imaging: a comprehensive update on principles and techniques. Korean J Radiol 2014; 15: 554–77.

40. Cantin S, Villien M, Moreaud O et al. Impaired cerebral vasoreactivity to CO2 in Alzheimer's disease using BOLD fMRI. Neuroimage 2011; 58: 579–87.

41. Bouvy WH, Geurts LJ, Kuijf HJ et al. Assessment of blood flow velocity and pulsatility in cerebral perforating arteries with 7-T quantitative flow MRI. NMR Biomed 2016; 29: 1295–304.

42. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.

43. Nasreddine ZS, Phillips NA, Bédirian V et al. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005; 53: 695–9.

44. Shi D, Chen X, Li Z. Diagnostic test accuracy of the Montreal cognitive assessment in the detection of post-stroke cognitive impairment under different stages and cutoffs: a systematic review and meta-analysis. Neurol Sci 2018; 39: 705–16.

45. Hamilton OKL, Backhouse EV, Janssen E et al. Cognitive impairment in sporadic cerebral small vessel disease: a systematic review and meta-analysis. Alzheimers Dement 2021; 17: 665–85.

46. Kloppenborg RP, Nederkoorn PJ, Geerlings MI, van den Berg E. Presence and progression of white matter hyperintensities and cognition: a meta-analysis. Neurology 2014; 82: 2127–38.

47. van den Berg E, Kloppenborg RP, Kessels RP, Kappelle LJ, Biessels GJ. Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: a systematic comparison of their impact on cognition. Biochim Biophys Acta 2009; 1792: 470–81.

48. Van Zandvoort MJ, De Haan EH, Kappelle LJ. Chronic cognitive disturbances after a single supratentorial lacunar infarct. Neuropsychiatry Neuropsychol Behav Neurol 2001; 14: 98–102.

49. Cremers LG, de Groot M, Hofman A et al. Altered tract-specific white matter microstructure is related to poorer cognitive performance: the Rotterdam study. Neurobiol Aging 2016; 39: 108–17.

50. Cremers LGM, Wolters FJ, de Groot M et al. Structural disconnectivity and the risk of dementia in the general population. Neurology 2020; 95: e1528–37.

51. Bushnell J, Svaldi D, Ayers MR et al. A comparison of techniques for deriving clustering and switching scores from verbal fluency word lists. Front Psychol 2022; 13: 743557. https://doi.org/10.3389/fpsyg.2022.743557.

52. Oyama A, Takeda S, Ito Y et al. Novel method for rapid assessment of cognitive impairment using high-performance eye-tracking technology. Sci Rep 2019; 9: 12932. https://doi.org/10.1038/s41598-019-49275-x.

53. Hachinski V, Iadecola C, Petersen RC et al. National Institute of Neurological Disorders and Stroke-Canadian stroke network vascular cognitive impairment harmonization standards. Stroke 2006; 37: 2220–41.

54. Brookes RL, Hollocks MJ, Khan U, Morris RG, Markus HS. The brief memory and executive test (BMET) for detecting vascular cognitive impairment in small vessel disease: a validation study. BMC Med 2015; 13: 51. https://doi.org/10.1186/s12916-015-0290-y.

55. Demeyere N, Riddoch MJ, Slavkova ED, Bickerton WL, Humphreys GW. The Oxford cognitive screen (OCS): validation of a stroke-specific short cognitive screening tool. Psychol Assess 2015; 27: 883–94.

56. Boyle PA, Yu L, Wilson RS, Leurgans SE, Schneider JA, Bennett DA. Person-specific contribution of neuropathologies to cognitive loss in old age. Ann Neurol 2018; 83: 74–83.

57. Yu L, Boyle PA, Leurgans S *et al.* Effect of common neuropathologies on progression of late life cognitive impairment. Neurobiol Aging 2015; 36: 2225–31.

58. Salvadó G, Brugulat-Serrat A, Sudre CH *et al.* Spatial patterns of white matter hyperintensities associated with Alzheimer's disease risk factors in a cognitively healthy middle-aged cohort. Alzheimers Res Ther 2019; 11: 12. https://doi.org/10.1186/s13195-018-0460-1.

59. van den Berg E, Geerlings MI, Biessels GJ, Nederkoorn PJ, Kloppenborg RP. White matter Hyperintensities and cognition in mild cognitive impairment and Alzheimer's disease: a domain-specific meta-analysis. J Alzheimers Dis 2018; 63: 515–27.

60. Kreisel SH, Blahak C, Bäzner H *et al.* Deterioration of gait and balance over time: the effects of age-related white matter change–the LADIS study. Cerebrovasc Dis 2013; 35: 544–53.

61. Group LS. 2001–2011: a decade of the LADIS (Leukoaraiosis and DISability) study: what have we learned about white matter changes and small-vessel disease? Cerebrovasc Dis 2011; 32: 577–88.

62. Yaqub A, Darweesh SKL, Dommershuijsen LJ *et al.* Risk factors, neuroimaging correlates and prognosis of the motoric cognitive risk syndrome: a population-based comparison with mild cognitive impairment. Eur J Neurol 2022; 29: 1587–99.

63. Okroglic S, Widmann CN, Urbach H, Scheltens P, Heneka MT. Clinical symptoms and risk factors in cerebral microangiopathy patients. PloS One 2013; 8: e53455. https://doi.org/10.1371/journal.pone.0053455.

64. van der Holst HM, Tuladhar AM, Zerbi V *et al.* White matter changes and gait decline in cerebral small vessel disease. Neuroimage Clin 2018; 17: 731–8.

65. Horak FB. Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? Age Ageing 2006; 35: ii7–11. https://doi.org/10.1093/ageing/afl077.

66. Chao YP, Cho KH, Yeh CH, Chou KH, Chen JH, Lin CP. Probabilistic topography of human corpus callosum using cytoarchitectural parcellation and high angular resolution diffusion imaging tractography. Hum Brain Mapp 2009; 30: 3172–87.

67. Cai M, Jacob MA, Norris DG, Duering M, de Leeuw FE, Tuladhar AM. Cognition mediates the relation between structural network efficiency and gait in small vessel disease. Neuroimage Clin. 2021; 30: 102667. https://doi.org/10.1016/j.nicl.2021.102667.

68. Su C, Yang X, Wei S, Zhao R. Association of Cerebral Small Vessel Disease with gait and balance disorders. Front Aging Neurosci 2022; 14: 834496. https://doi.org/10.3389/fnagi.2022.834496.

69. Blahak C, Baezner H, Pantoni L *et al.* Deep frontal and periventricular age related white matter changes but not basal ganglia and infratentorial hyperintensities are associated with falls: cross sectional results from the LADIS study. J Neurol Neurosurg Psychiatry 2009; 80: 608–13.

70. Kim YJ, Kwon HK, Lee JM *et al.* Gray and white matter changes linking cerebral small vessel disease to gait disturbances. Neurology 2016; 86: 1199–207.

71. Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: a systematic review. Lancet Neurol 2007; 6: 611–9.

72. de Laat KF, van den Berg HA, van Norden AG, Gons RAR, Olde Rikkert MGM, de Leeuw FE. Microbleeds are independently related to gait disturbances in elderly individuals with cerebral small vessel disease. Stroke 2011; 42: 494–7.

73. Choi P, Ren M, Phan TG *et al.* Silent infarcts and cerebral microbleeds modify the associations of white matter lesions with gait and postural stability: population-based study. Stroke 2012; 43: 1505–10.

74. van Dalen JW, Moll van Charante EP, Nederkoorn PJ, van Gool WA, Richard E. Poststroke apathy. Stroke 2013; 44: 851–60.

75. Clancy U, Gilmartin D, Jochems ACC, Knox L, Doubal FN, Wardlaw JM. Neuropsychiatric symptoms associated with cerebral small vessel disease: a systematic review and meta-analysis. Lancet Psychiatry 2021; 8: 225–36.

76. Maclullich AM, Ferguson KJ, Miller T, de Rooij SE, Cunningham C. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. J Psychosom Res 2008; 65: 229–38.

77. Siejka TP, Srikanth VK, Hubbard RE *et al.* White matter Hyperintensities and the progression of frailty-the Tasmanian study of cognition and gait. J Gerontol A Biol Sci Med Sci 2020; 75: 1545–50.

78. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of Adl: a standardized measure of biological and psychosocial function. JAMA 1963; 185: 914–9.

79. Guralnik JM, Simonsick EM, Ferrucci L *et al.* A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994; 49: M85–94. https://doi.org/10.1093/geronj/49.2.M85.

80. Wardlaw JM, Debette S, Jokinen H *et al.* ESO guideline on covert cerebral small vessel disease. Eur Stroke J 2021; 6: CXI–CLXII. https://doi.org/10.1177/23969873211012132.

81. Areosa SA, Grimley EV. Effect of the treatment of type II diabetes mellitus on the development of cognitive impairment and dementia. Cochrane Database Syst Rev 2002; 4: CD003804.

82. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. Cochrane Database Syst Rev 2016; 2016: CD003160. https://doi.org/10.1002/14651858.CD003160.pub3.

83. Group SMIftSR, Williamson JD, Pajewski NM *et al.* Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. JAMA 2019; 321: 553–61.

84. den Brok M, van Dalen JW, Abdulrahman H *et al.* Antihypertensive medication classes and the risk of dementia: a systematic review and network meta-analysis. J Am Med Dir Assoc 2021; 22: 1386–1395.e15.

85. Kivipelto M, Mangialasche F, Snyder HM *et al.* Worldwide FINGERS network: a global approach to risk reduction and prevention of dementia. Alzheimers Dement 2020; 16: 1078–94.