Progress towards standardised diagnosis of vascular cognitive impairment: guidelines from the vascular impairment of cognition classification consensus study (VICCCS)

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Abstract

INTRODUCTION: Progress in understanding and management of vascular cognitive impairment (VCI) has been hampered by lack of consensus on diagnosis, reflecting the use of multiple different assessment protocols. A large multinational group of clinicians and researchers participated in a two-phase Vascular Impairment of Cognition Classification Consensus study (VICCCS) to agree on principles (VICCCS-1) and protocols (VICCCS-2) for diagnosis of VCI. We present VICCCS-2.

METHODS: We used VICCCS-1 principles and published diagnostic guidelines as points of reference for an online Delphi survey aimed at achieving consensus on clinical diagnosis of VCI.

RESULTS: Six survey rounds comprising 65-79 participants agreed guidelines for diagnosis of VICCCS-revised Mild and Major forms of VCI and endorsed the National Institute of Neurological Disorders-Canadian Stroke Network (NINDS-CSN) neuropsychological assessment protocols and recommendations for imaging.

DISCUSSION: VICCCS-2 suggests standardised use of NINDS-CSN recommendations on neuropsychological and imaging assessment for diagnosis of VCI so as to promote research collaboration.

1. Introduction

Since Hachinski et al [1] proposed the term multi-infarct dementia to describe dementia complicating ischaemic vascular disease, numerous other descriptors have been used to encompass the heterogeneous clinical and aetiological spectrum of cognitive impairment due to cerebrovascular disease (CVD). These include vascular dementia (VaD), vascular cognitive impairment (VCI), subcortical (ischaemic) vascular dementia, and vascular cognitive disorder, variably diagnosed according to multiple different guidelines or protocols [2-14], some agreed by national institutions or

research networks, e.g. Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) [11],
International Statistical Classification of Diseases, 10th Revision (ICD-10) [15], the National Institute
of Neurological Disorders and Stroke—Association Internationale pour la Recherche et
l'Enseignement en Neurosciences (NINDS-AIREN) [16], and Diagnostic and Statistical Manual of
Mental Disorders (DSM) fourth and fifth editions [17, 18].

Studies comparing some of these protocols have shown they are not readily interchangeable [19-21]. After the commencement of the vascular impairment of cognition classification consensus study phase 1 (VICCCS-1), the American Heart Association/American Stroke Association (AHA/ASA) published a statement on vascular contributions to cognitive impairment and dementia [22]. This supported the use of assessment protocols previously published by NINDS-Canadian Stroke Network (CSN) [13]. There have been other recent contributions to this field from the International Society of Vascular Behavioural and Cognitive Disorders (VASCOG) [23] and in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [18]. The level of take up of these recent guidelines is still unclear. Only those published during VICCCS-1, before commencement of VICCCS-2, could be included for consideration in the present study [22, 24].

The aim of VICCCS was to achieve broad international consensus on diagnosis of VCI, through participation of a large pool of international researchers and clinicians in an iterative survey using the Delphi approach. After two initial survey rounds, the study was separated into two phases: VICCCS-1, addressing key concepts in our understanding and terminology of cognitive impairment resulting from CVD [25], and VICCCS-2, focussing on the formulation of practical guidelines for diagnosis.

VICCCS-1 achieved broad consensus on concepts of VCI. It supported the use of 'Mild' and 'Major' subdivisions of the severity of impairment, aligning with the revised terminology in DSM-5. VICCCS-1

participants concluded that attempts to separate Mild VCI into further subtypes according to affected cognitive domains were at present premature, but agreed that this should be an area of future research. VICCCS-1 agreed (see Figure 1, reproduced from [25]) that the Major forms of VCI (VaD) should be classified into 4 main subtypes: i) post-stroke dementia (PSD); ii) subcortical ischaemic vascular dementia (SIVaD); iii) multi-infarct (cortical) dementia (MID); and iv) mixed dementias (further subdivided according to additional neurodegenerative pathologies). Framed by these concepts, VICCCS-2 used the same Delphi methodology to agree diagnostic guidelines on determination of severity of VCI, and discrimination of subtypes.

2. Methods

Participants in VICCCS-1 [25] were invited to participate in VICCCS-2 (supplementary figure 1). While 149 initially agreed to participate, only approximately half were active and committed respondents in three or more rounds, with low attrition and little variation in participation through the six rounds (65-79 participants in each round, a mean of 72). Of the active participants, 63-75% (mean 68%) were clinicians with direct involvement in clinical assessment or health service patient care. The remainder were non-clinical (i.e. supporting clinical work technically or otherwise, but not involved in clinical decision making, or predominantly involved in research). Individual round representation is provided in Supplementary table 1.

2.1 Data collection

We used the Delphi method, an iterative, multi-staged series of structured questionnaires with feedback of anonymised responses, and progressive refinement of questions to reach consensus [26]. The process was co-ordinated by a non-participating researcher (O.A.S). Anonymisation of responses facilitated free expression of opinion throughout the study. The feedback of summary

responses after each round informed subsequent questions and allowed unbiased evolution of group judgement. A threshold of two-thirds agreement was chosen to signify consensus [27] for issues refined iteratively through multiple rounds, as in VICCCS-1 [25]. For issues where this threshold was not reached, we present the summary data including the view that was most strongly supported. A summary of topics covered in each Delphi round is presented in Figure 2. The first two rounds were used to select from previous publications those diagnostic criteria deemed most valuable as a basis for further discussion. These provided main themes addressed in the four subsequent rounds (November 2012 – September 2013). Consensus views from topics addressed in VICCCS-1 were utilised in discussions.

3. Results

3.1 VICCCS foundation rounds and VICCCS-2 rounds 1 & 2

In the two foundation rounds of VICCCS the consensus view (94% of respondents) was that none of the current diagnostic protocols was fully fit for purpose and that formulation of improved assessment criteria for VCI was a priority. Data from the foundation rounds, including the researcher-led [2, 6, 7, 11-14, 16, 28-30] and organisation-based diagnostic criteria/protocols that were critiqued by the participants, are provided as supplementary material.

Participants selected their preferred criteria of the six presented (4 chosen as best starting points in VICCCS foundation rounds [6, 12, 13, 31] and 2 that were published during VICCCS-1 and could therefore be critiqued in VICCCS-2 [22, 24]). Of these six, the AHA/ASA Scientific Statement: vascular contributions to cognitive impairment and dementia [22], henceforth referred to as AHA/ASA, was the first preference of the highest proportion of respondents (41%), followed by NINDS-CSN [13] (25%). The AHA/ASA does not provide assessment protocols but refers to the recommendations made in the NINDS-CSN. These guidelines provided the basis for further discussion and elaboration.

According to most respondents (65%), VICCCS-2 aimed to provide a single set of diagnostic guidelines for clinical and research use. Agreed objectives were to develop a clear and efficient protocol that was simple to use and would yield readily interpretable results, allowing discrimination of VCI subtypes and severity.

3.2 VICCCS-2 rounds 3-6

3.2.1 Measure of severity - differentiating between Mild and Major VCI

In VICCCS-1 round 4, participants considered the cognitive domains that needed assessment to measure the severity of VCI. These were reviewed in VICCCS-2 round 3, in which 94% agreed that the core domains for assessment should be executive function, attention, memory, language, and visuospatial function. The domains of learning, neuropsychiatry, and social cognition should be treated as optional, outside of the core assessment, unless and until there is stronger evidence for their inclusion. No other domains (including abstraction, agnosia, emotionality, praxis, and processing or psychomotor speed) were supported as core domains; for some, respondents thought there were insufficient tools for assessment (e.g. apraxia, that features in NINDS-CSN: 80% of respondents).

Eighty-one percent of VICCCS-1 respondents felt the differentiation between Mild and Major VCI (VaD) should be based on the number of domains affected and that both IADL and ADL were necessary determinants. In VICCCS-2 round 3, a consensus (85%) definition was achieved for *Mild VCI: impairment in at least one cognitive domain, and mild to no impairment in IADL/ADL, respectively (independent of the motor/sensory sequelae of the vascular event)*. In rounds 3 and 4 several definitions were considered for Major VCI (VaD) but no overall majority was achieved for any one option. On further examination of the various choices, 71% had chosen a definition that

included the word "severe" and 73% had chosen an option with "at least ONE cognitive domain" (rather than "at least TWO cognitive domains"). These observations were presented to the participants in round 5, and they were asked to choose between the three most-favoured definitions from the previous round. There was 60% support for the Major VCI (VaD) definition: severe deficits in at least ONE cognitive domain (other deficits may be present in multiple domains) and severe disruption to IADL/ADL (independent of the motor/sensory sequelae of the vascular event).

Consensus-level (67%) support was obtained for a definition requiring deficits in one rather than two cognitive domains and for inclusion of the descriptor "severe". Those who did not support the mandatory inclusion of the descriptor "severe" highlighted the important issue of people with moderate cognitive impairment, and suggested the use of the term "significant" to allow greater clinical discretion and flexibility. The scenario of "... the case of the very bright patient whose functioning is severely compromised but still does ok on rudimentary cognitive assessment" was given as an illustrative example.

On feedback of the results of round 5, participants were asked to consider an amendment of the definition of Major VCI (VaD) by substitution of "severe" with "significant", i.e. clinically significant deficits in at least one cognitive domain (other deficits may be present in multiple domains) and severe disruption to IADL/ADL (independent of the motor/sensory sequelae of the vascular event). 52% were in favour, and support for the most popular definition in round 5 – severe deficits in at least one cognitive domain (other deficits may be present in multiple domains) and severe disruption to IADL/ADL (independent of the motor/sensory sequelae of the vascular event) – had dropped to 34%. Although our pre-defined consensus level (67%) was not reached for any definition in either round, it was clear that some qualification of the severity of deficit in at least one cognitive domain was preferred. Therefore, the proposed definition (representing the majority view) for *Major VCI (VaD)* is: *clinically significant deficits in at least one cognitive domain (other deficits may*

be present in multiple domains) and severe disruption to IADL/ADL (independent of the motor/sensory sequelae of the vascular event).

3.2.2 Clinical evaluation and time-frame for assessment

Recommendations of the NINDS-CSN abbreviated clinical evaluation of VCI were strongly supported by round 3 respondents (86%). However, NINDS-CSN recommendations differ for research and clinical settings, and most round 2 respondents (77%) thought the priority should be to agree a core of assessments for both research and clinical use, with the option of additional assessments for local use in either a clinical or research context.

It was agreed that a neuropsychological assessment protocol for use in a typical clinical diagnostic setting, noting time pressures and patient group capabilities, should take 60 minutes at most, although optional assessments could take additional time. The inclusion of all core items in the NINDS-CSN 60-minute protocol was supported by most round 3 respondents. Only the MMSE supplementary test was supported by most respondents (71%). Other supplemental tests -- Rey-Osterrieth Complex Figure, Boston Naming Test and Digit Symbol-Coding Incidental Learning – did not achieve consensus support for inclusion. All core and supplementary items in the NINDS-CSN 30-minute protocol were also supported (Table 1).

3.2.3 The role of aphasia in diagnosis of VCI

VICCCS-2 round 2 respondents agreed (72%) with the AHA/ASA statement on aphasia: "Severity of aphasia precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (e.g. annual cognitive evaluations) before the clinical event that caused aphasia could be classified as having probable VaD/VaMCI."[22]. In round 4, respondents agreed (96%) on the qualifying sentence "that the assessment of IADL/ADL should be made where

possible". 68% of round 4 participants felt that "probable Mild VCI or probable Major VCI" was the appropriate classification of cases with aphasia when imaging was available, and "possible" used in cases of aphasia when imaging was not available (90%).

3.2.4 Those at risk of VCI

One of the agreed principles in VICCCS-1 [25] was: "The new VCI construct recognises the importance of people who are at risk of VCI, however, their consideration should be contingent upon the presentation of a sustained level of impairment even if in a very mild form as opposed to impairment that can be transient or revert to normal levels". Respondents agreed (96%) that people at risk of VCI should be given greater consideration for diagnosis if at least 6 months of sustained impairment is present. 88% also agreed that in those at risk of VCI, other potential causes of sustained impairment (e.g. depression or vitamin D deficiency), in addition to the already agreed exclusions from diagnosis (i.e. drug/alcohol abuse/dependence within 3 last months of first recognition of impairment or delirium) should have been excluded. Caregiver reporting (88%) and clinical observation (73%) were supported mechanisms to collect this information. Screening-type assessment (49%) and more detailed formal assessment (43%) were not supported by the majority.

3.2.5 Possible and Probable terms in VCI and 'Mixed dementias' subgroup

In the AHA/ASA, which served as a starting point to discuss the use of the terms 'possible' and 'probable' VCI, only the categories of 'possible' VaD or VaMCI allowed the inclusion of other phenotypes (e.g. evidence of other neurodegenerative disorders). The AHA/ASA also does not provide separate diagnosis or allow delineation of further subgroups of patients (e.g. the comorbidities present in mixed dementias). In VICCCS-1 the consensus was that VCI should contain a standalone umbrella-like subgroup termed "mixed dementias". VICCCS-1 participants also agreed that this subgroup could comprise further groupings that included patients with specific combinations of phenotypes, each of which would be specifically named where possible (e.g. VCI-AD

if there is evidence of both VCI and AD). Furthermore, it was agreed that the order of the descriptive phenotypic terms relevant to patients should attempt to reflect the relative contribution of phenotypes present, i.e. AD-VCI, or VCI-AD, to the extent that discrimination was possible.

On consideration of differences between the AHA/ASA and VICCCS-1, VICCCS-2 round 2 respondents agreed (92%) that the diagnostic guidelines should attempt to incorporate the VICCCS-proposed "mixed dementias" as a separate distinct diagnostic subgroup of Major VCI, and 'probable' or 'possible' are to be used to differentiate the level of diagnostic evidence to help classify patients for both Major VCI (VaD) subgroups (81%) and Mild VCI (70%).

3.2.6 Incorporating temporal relationships in VCI diagnosis

In AHA/ASA a clear temporal relationship between a vascular event and onset of cognitive deficits is required for a 'probable' diagnosis. In VICCCS-1, the definition of PSD – an agreed subgroup of major VCI (VaD), required that cognitive decline develop within 6 months of stroke. However, temporal relationships were not discussed for other subtypes of VCI. In VICCCS-2, respondents thought that a clear temporal relationship between a vascular event and onset of cognitive deficits should not be an essential component for diagnosis of Mild VCI (77%), (SIVaD) (88%), mixed dementias (85%) or MID (74%).

3.2.7 The role of imaging in VCI diagnosis

In VICCCS-2 round 3, the consensus was that imaging evidence of CVD was essential for diagnosis of Major VCI (VaD) (86%) and Mild VCI (79%). In round 4, although most respondents felt the NINDS-CSN recommendations were possible/appropriate in the respondents' clinical settings (75% MRI / 81% CT), 93% thought that the "acceptable MRI measures" proposed in NINDS-CSN should be the core recommendation for imaging in clinical settings, and the "recommended MRI measures"

supported as additional measures for use in either clinical or research contexts (Table 2 and 3).

Several respondents stated that CT might be insensitive or insufficient to detect small vessel disease or evaluate vascular status. The limitations of CT for VCI are also highlighted in NINDS-CSN. In round 4, respondents agreed (93%) that MRI should be the gold-standard imaging for VCI and 90% agreed that CT should be used only if MRI were not available or deemed too costly. This would also apply to cases where MRI is contraindicated. A consensus (68%) was reached on the use of the term "possible" Mild VCI or Major VCI if neither MRI nor CT imaging were available. Yet 89% felt that "probable" was the appropriate diagnostic category if only CT imaging were available.

Majority support (67%) was not reached for any of the other "future" imaging methods described in NINDS-CSN, and the consensus was that none of these is ready for inclusion in clinical diagnosis.

A summary of VICCCS diagnosis guidelines is provided in Panel 1.

4. Discussion

VICCCS-2 has provided new consensus-based guidelines for diagnosis of Mild and Major VCI (VaD) as previously defined [25], with AHA/ASA and NINDS-CSN guidelines as reference points for discussions. Clinical evaluation and neuropsychological protocols in the NINDS-CSN were supported for use by VICCCS respondents. The "acceptable MRI measures" outlined in NINDS-CSN should be the core recommendation for imaging in clinical settings. In terms of assessing severity, VICCCS diagnosis guidelines specify deficits in at least 1 domain, with clinically significant cognitive deficits of sufficient severity (moderate to severe) and severe deficits in IADL/ADL differentiating Major from Mild forms. Patients with PSD, SIVaD, MID and mixed dementias should also be subcategorised and any comorbid neurodegenerative disease recorded.

4.1 Comparison of VICCCS with recently published guidelines

VICCCS was conducted between 2010 and 2013, which coincided with the development of DSM-5 and VASCOG criteria for Vascular Cognitive Disorders (VCD) [23]. VICCCS participants provided collective feedback on draft DSM-5 proposals that were made available prior to their finalisation, through a tailored survey developed (by O.A.S), in consultation with P.S. acting on behalf of the DSM-5 Neurocognitive Disorders Work Group. VICCCS respondents agreed that the Mild and Major terminologies proposed in DSM-5 were helpful and should be adopted in VICCCS. The VASCOG criteria are also aligned with DSM-5 [23].

In terms of assessing severity, both AHA/ASA and VICCCS specify the same core domains for assessment. In VASCOG, visuoconstructional-perceptual ability, praxis-gnosis-body schema and social cognition are additionally tested. The definitions of Mild VCI are comparable; however, they are not sub-categorised in VICCCS as respondents felt more evidence was needed. The definition of major forms of VCI in VICCCS and VASCOG requires deficits in at least 1 domain, rather than 2 domains as specified in AHA/ASA. Loss of independence in IADL is the threshold in VASCOG and DSM-5. In VICCCS-1, assessment of both IADL and ADL was deemed necessary to determine severity. Patients with PSD, SIVaD and MID are also subcategorised in VICCCS but not specified in AHA/ASA, although subtypes in VASCOG include cortical-subcortical and subcortical ischaemic. The AHA/ASA category of "Unstable VaMCI", for cases which revert to normal from VaMCI, was not supported by VICCCS respondents.

One of the main differences between VICCCS and AHA/ASA is the VICCCS subcategorisation of patients with comorbid pathologies, seen to be important, under the umbrella term "mixed dementias" but with the types of pathologies specified. Improvements in the accuracy of this would be an important goal of any future operational diagnostic protocols, for which research into biomarkers may be helpful [32]. AHA/ASA does not delineate these subgroups of patients, with only the categories of 'possible' VaD or VaMCI allowing the inclusion of other phenotypes (e.g. evidence

of other neurodegenerative disorders). VASCOG criteria encompass categories of multiple causation, including VCD with concomitant AD (Major or Mild) and VCD with additional pathology: e.g. Lewy body disease.

In VICCCS, the use of probable and possible terms is reserved for the strength of evidence to support diagnosis. One such example of supportive evidence is a clear temporal relationship between a vascular event and onset of cognitive deficits in PSD, which is differentiated from other forms of VCI by the onset of symptoms within six months of stroke. Another is the imaging of CVD. VICCCS respondents concluded that MRI is the gold standard for imaging. If CT were the only means available, only a 'probable' diagnosis could be made, and only a diagnosis of 'possible' if no imaging evidence were available. The recent STRIVE imaging criteria for small vessel disease [33] published after the completion of our study, aligned with VICCCS' conceptualisation for SIVaD, warrant consideration in future validations of VICCCS-2. VICCCS supports and expands on the AHA/ASA guidance on patients with aphasia, in whom assessment of IADL/ADL should be made when possible, allowing diagnosis of 'probable' with imaging evidence or 'possible' without it.

4.2 Limitations and future work

The use of online Delphi surveys in VICCCS allowed flexible and confidential participation amongst an unprecedented number of international participants over an extended period [25, 26, 34]. The guidelines reflect considered opinion since there was little participant attrition between rounds (90-97% of participants responding over rounds 2-6), reflecting sustained engagement, with most topics addressed over multiple rounds.

Given the large number of respondents and their broad interdisciplinarity, it is noteworthy that we achieved consensus on most topics addressed in VICCCS. Reaching consensus was most challenging

for the definition of Major VCI (VaD), perhaps reflecting residual sensitivities associated with this diagnosis and associated implications for health and social care services. Consequently, specific thresholds of severity of impairment were not established. VICCCS-1 concluded that subtyping of Mild VCI may be worthwhile but required more research [25], a view supported in a recent study that highlighted the importance of harmonising neuropsychological test score levels for defining impairment [35]. Inclusion of defined thresholds of severity of impairment within the neuropsychological test battery and IADL/ADL may help to guide the differentiation of VCI subtypes in clinical settings. Support for the continued use of MMSE [36] may be surprising, given that MoCA [37] has been shown to be an equivalent or more sensitive test for the detection of VCI, ([38, 39], for example). It is noteworthy that only 23% of respondents indicated use of the NINDS-CSN 5-minute protocol, (see Supplementary information), whilst NINDS-CSN endorsed the full as well as the short MoCA. The use of biomarkers and advances in imaging criteria, [33, 40, 41], including the use of arterial spin labelling-MRI [42, 43], may refine the subtyping of Mild and Major VCI. Further work is needed on imaging protocols, including measurement of grey matter atrophy, cortical thinning or global atrophy in the context of suspected VCI [44, 45]. Given the presence of vascular pathologies in apparent cognitively normal elderly people, recent progress in establishing neuropathological diagnostic criteria for assessing the likelihood that CVD contributed to pre-mortem cognitive impairment [46] is likely to have an important role in the validation of future pre-mortem diagnostic approaches. Translational models and genetic studies may provide further insight into the pathological mechanisms and possible therapeutic targets for VCI [47]. A multimodal strategy for treatment of VCI, incorporating both non-pharmacological therapies, such as Transcranial Magnetic Stimulation ([48], for review], and pharmacological treatment, has been proposed [49].

5. Conclusions

We present a consensus-based set of guidelines for diagnosing VCI, supported by a large multinational group of researchers. VICCCS guidelines have drawn upon, critiqued, expanded and refined previous efforts. We hope that they will be widely adopted, to improve consistency in diagnosis and standardisation in VCI research. This would allow better comparison of findings across studies and facilitate large-scale collaborative research on a group of diseases that despite modest prevalence and considerable heterogeneity have major societal impact.

6. Acknowledgements

6.1 Contributors

OAS was the study coordinator, analysed the data, formulated the questionnaires and wrote the manuscript. PGK was Chief investigator, conceived and designed the study, obtained the necessary funding, reviewed each round data, formulated the questionnaires and wrote the manuscript. YB-S, APP, SL were Co-investigators and members of the Steering Group. Other listed authors were members of the Steering Group who reviewed the content of the pilot questionnaires, draft and final manuscript and were participants in the study. Authors listed under the banner of VICCCS groups contributed to data gathering in multiple survey rounds and approved the final submitted version of the paper.

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7. References

- [1] Hachinski, V.C., N.A. Lassen, and J. Marshall. Multi-infarct dementia. A cause of mental deterioration in the elderly. Lancet 1974; 2(7874): 207-10.
- [2] Kalaria, R.N., R.A. Kenny, C.G. Ballard, R. Perry, P. Ince, and T. Polvikoski. Towards defining the neuropathological substrates of vascular dementia. J Neurol Sci 2004; 226(1-2): 75-80.
- [3] Sachdev, P. Vascular cognitive disorder. Int J Geriatr Psychiatry 1999; 14(5): 402-3.
- [4] Rockwood, K., C. Macknight, C. Wentzel, S. Black, R. Bouchard, S. Gauthier, H. Feldman, D. Hogan, A. Kertesz, and P. Montgomery. The diagnosis of "mixed" dementia in the Consortium for the Investigation of Vascular Impairment of Cognition (CIVIC). Ann N Y Acad Sci 2000; 903: 522-8.
- [5] O'Brien, J.T., T. Erkinjuntti, B. Reisberg, G. Roman, T. Sawada, L. Pantoni, J.V. Bowler, C. Ballard, C. DeCarli, P.B. Gorelick, K. Rockwood, A. Burns, S. Gauthier, and S.T. DeKosky. Vascular cognitive impairment. Lancet Neurology 2003; 2(2): 89-98.
- [6] Zhao, Q.L., Y. Zhou, Y.L. Wang, K.H. Dong, and Y.J. Wang. A new diagnostic algorithm for vascular cognitive impairment: the proposed criteria and evaluation of its reliability and validity. Chin Med J (Engl) 2010; 123(3): 311-9.

- [7] Cao, X., Q. Guo, Q. Zhao, L. Jin, J. Fu, and Z. Hong. The neuropsychological characteristics and regional cerebral blood flow of vascular cognitive impairment-no dementia. Int J Geriatr Psychiatry 2010; 25(11): 1168-76.
- [8] Hachinski, V.C. and J.V. Bowler. Vascular dementia. Neurology 1993; 43(10): 2159-60; author reply 2160-1.
- [9] Roman, G.C., P. Sachdev, D.R. Royall, R.A. Bullock, J.M. Orgogozo, S. Lopez-Pousa, R. Arizaga, and A. Wallin. Vascular cognitive disorder: a new diagnostic category updating vascular cognitive impairment and vascular dementia. Journal of the Neurological Sciences 2004; 226(1-2): 81-87.
- [10] Rockwood, K., C. Wentzel, V. Hachinski, D.B. Hogan, C. MacKnight, and I. McDowell. Prevalence and outcomes of vascular cognitive impairment. Vascular Cognitive Impairment Investigators of the Canadian Study of Health and Aging. Neurology 2000; 54(2): 447-51.
- [11] Chui, H.C., J.I. Victoroff, D. Margolin, W. Jagust, R. Shankle, and R. Katzman. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology 1992; 42(3 Pt 1): 473-80.
- [12] Erkinjuntti, T., D. Inzitari, L. Pantoni, A. Wallin, P. Scheltens, K. Rockwood, G.C. Roman, H. Chui, and D.W. Desmond. Research criteria for subcortical vascular dementia in clinical trials. J Neural Transm Suppl 2000; 59: 23-30.
- [13] Hachinski, V., C. Iadecola, R.C. Petersen, M.M. Breteler, D.L. Nyenhuis, S.E. Black, W.J. Powers, C. DeCarli, J.G. Merino, R.N. Kalaria, H.V. Vinters, D.M. Holtzman, G.A. Rosenberg, A. Wallin, M. Dichgans, J.R. Marler, and G.G. Leblanc. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke 2006; 37(9): 2220-41.
- [14] Hachinski, V.C., L.D. Iliff, E. Zilhka, G.H. Du Boulay, V.L. McAllister, J. Marshall, R.W. Russell, and L. Symon. Cerebral blood flow in dementia. Arch Neurol 1975; 32(9): 632-7.
- [15] World Health Organization. Diagnostic criteria for research. The ICD-10 classification of mental and behavioural disorders. 1993, Geneva: World Health Organization
- [16] Roman, G.C., T.K. Tatemichi, T. Erkinjuntti, J.L. Cummings, J.C. Masdeu, J.H. Garcia, L. Amaducci, J.M. Orgogozo, A. Brun, A. Hofman, and et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993; 43(2): 250-60.
- [17] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. 1994: Washington, DC: American Psychiatric Association.
- [18] American Psychiatric Association Diagnostic and statistical manual of mental disorders (5th ed.). 2013, American Psychiatric Publishing, Arlington.
- [19] Chui, H.C., W. Mack, J.E. Jackson, D. Mungas, B.R. Reed, J. Tinklenberg, F.L. Chang, K. Skinner, C. Tasaki, and W.J. Jagust. Clinical criteria for the diagnosis of vascular dementia: a multicenter study of comparability and interrater reliability. Arch Neurol 2000; 57(2): 191-6.
- [20] Wiederkehr, S., M. Simard, C. Fortin, and R. van Reekum. Validity of the clinical diagnostic criteria for vascular dementia: a critical review. Part II. J Neuropsychiatry Clin Neurosci 2008; 20(2): 162-77.
- [21] Pohjasvaara, T., R. Mantyla, R. Ylikoski, M. Kaste, and T. Erkinjuntti. Comparison of different clinical criteria (DSM-III, ADDTC, ICD-10, NINDS-AIREN, DSM-IV) for the diagnosis of vascular dementia. National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences. Stroke 2000; 31(12): 2952-7.
- [22] Gorelick, P.B., A. Scuteri, S.E. Black, C. Decarli, S.M. Greenberg, C. Iadecola, L.J. Launer, S. Laurent, O.L. Lopez, D. Nyenhuis, R.C. Petersen, J.A. Schneider, C. Tzourio, D.K. Arnett, D.A. Bennett, H.C. Chui, R.T. Higashida, R. Lindquist, P.M. Nilsson, G.C. Roman, F.W. Sellke, S. Seshadri, C.o.E. American Heart Association Stroke Council, C.o.C.N.C.o.C.R. Prevention, Intervention, S. Council on Cardiovascular, and Anesthesia. Vascular contributions to

- cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke 2011; 42(9): 2672-713.
- [23] Sachdev, P., R. Kalaria, J. O'Brien, I. Skoog, S. Alladi, S.E. Black, D. Blacker, D.G. Blazer, C. Chen, H. Chui, M. Ganguli, K. Jellinger, D.V. Jeste, F. Pasquier, J. Paulsen, N. Prins, K. Rockwood, G. Roman, P. Scheltens, B. Internationall Society for Vascular, and D. Cognitive. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. Alzheimer Dis Assoc Disord 2014; 28(3): 206-18.
- [24] Hachinski, V., S. Oveisgharan, A.K. Romney, and W.R. Shankle. Optimizing the Hachinski Ischemic Scale. Arch Neurol 2012; 69(2): 169-75.
- [25] Skrobot, O.A., J. O'Brien, S. Black, C. Chen, C. DeCarli, T. Erkinjuntti, G.A. Ford, R.N. Kalaria, L. Pantoni, F. Pasquier, G.C. Roman, A. Wallin, P. Sachdev, I. Skoog, V. group, Y. Ben-Shlomo, A.P. Passmore, S. Love, and P.G. Kehoe. The Vascular Impairment of Cognition Classification Consensus Study. Alzheimers Dement 2016.
- [26] Dalkey, N. and O. Helmer. An Experimental Application of the Delphi Method to the Use of Experts. Management Science 1963; 9(3): 458-467.
- [27] Alexandrov, A.V., P.M. Pullicino, E.M. Meslin, and J.W. Norris. Agreement on disease-specific criteria for do-not-resuscitate orders in acute stroke. Members of the Canadian and Western New York Stroke Consortiums. Stroke 1996; 27(2): 232-7.
- [28] Rosen, W.G., R.D. Terry, P.A. Fuld, R. Katzman, and A. Peck. Pathological verification of ischemic score in differentiation of dementias. Ann Neurol 1980; 7(5): 486-8.
- [29] Knopman, D.S., W.A. Rocca, R.H. Cha, S.D. Edland, and E. Kokmen. Incidence of vascular dementia in Rochester, Minn, 1985-1989. Arch Neurol 2002; 59(10): 1605-10.
- [30] Price, C.C., A.L. Jefferson, J.G. Merino, K.M. Heilman, and D.J. Libon. Subcortical vascular dementia: integrating neuropsychological and neuroradiologic data. Neurology 2005; 65(3): 376-82
- [31] Roman, G.C., T.K. Tatemichi, T. Erkinjuntti, J.L. Cummings, J.C. Masdeu, J.H. Garcia, L. Amaducci, J.M. Orgogozo, A. Brun, A. Hofman, D.M. Moody, M.D. Obrien, T. Yamaguchi, J. Grafman, B.P. Drayer, D.A. Bennett, M. Fisher, J. Ogata, E. Kokmen, F. Bermejo, P.A. Wolf, P.B. Gorelick, K.L. Bick, A.K. Pajeau, M.A. Bell, C. Decarli, A. Culebras, A.D. Korczyn, J. Bogousslavsky, A. Hartmann, and P. Scheinberg. VASCULAR DEMENTIA DIAGNOSTIC-CRITERIA FOR RESEARCH STUDIES REPORT OF THE NINDS-AIREN INTERNATIONAL WORKSHOP. Neurology 1993; 43(2): 250-260.
- [32] Wallin, A., E. Kapaki, M. Boban, S. Engelborghs, D.M. Hermann, B. Huisa, M. Jonsson, M.G. Kramberger, L. Lossi, B. Malojcic, S. Mehrabian, A. Merighi, E.B. Mukaetova-Ladinska, G.P. Paraskevas, B.O. Popescu, R. Ravid, L. Traykov, G. Tsivgoulis, G. Weinstein, A. Korczyn, M. Bjerke, and G. Rosenberg. Biochemical markers in vascular cognitive impairment associated with subcortical small vessel disease A consensus report. BMC Neurol 2017; 17(1): 102.
- [33] Wardlaw, J.M., E.E. Smith, G.J. Biessels, C. Cordonnier, F. Fazekas, R. Frayne, R.I. Lindley, J.T. O'Brien, F. Barkhof, O.R. Benavente, S.E. Black, C. Brayne, M. Breteler, H. Chabriat, C. Decarli, F.E. de Leeuw, F. Doubal, M. Duering, N.C. Fox, S. Greenberg, V. Hachinski, I. Kilimann, V. Mok, R. Oostenbrugge, L. Pantoni, O. Speck, B.C. Stephan, S. Teipel, A. Viswanathan, D. Werring, C. Chen, C. Smith, M. van Buchem, B. Norrving, P.B. Gorelick, M. Dichgans, and S.T.f.R.V.c.o. nEuroimaging. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013; 12(8): 822-38.
- [34] Delbecq, A.L., Van de Ven, A. H., & Gustafson, D. H., Group techniques for program planning. . 1975: Glenview, IL: Scott, Foresman, and Co. .
- [35] Salvadori, E., A. Poggesi, R. Valenti, G. Pracucci, F. Pescini, M. Pasi, S. Nannucci, S. Marini, A. Del Bene, L. Ciolli, A. Ginestroni, S. Diciotti, G. Orlandi, I. Di Donato, N. De Stefano, M. Cosottini, A. Chiti, A. Federico, M.T. Dotti, U. Bonuccelli, D. Inzitari, L. Pantoni, and V.M.-T.S. Group. Operationalizing mild cognitive impairment criteria in small vessel disease: the VMCI-Tuscany Study. Alzheimers Dement 2016; 12(4): 407-18.

- [36] Folstein, M.F., S.E. Folstein, and P.R. McHugh. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12(3): 189-98.
- [37] Nasreddine, Z.S., N.A. Phillips, V. Bedirian, S. Charbonneau, V. Whitehead, I. Collin, J.L. Cummings, and H. Chertkow. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005; 53(4): 695-9.
- [38] Dong, Y., V.K. Sharma, B.P. Chan, N. Venketasubramanian, H.L. Teoh, R.C. Seet, S. Tanicala, Y.H. Chan, and C. Chen. The Montreal Cognitive Assessment (MoCA) is superior to the Mini-Mental State Examination (MMSE) for the detection of vascular cognitive impairment after acute stroke. J Neurol Sci 2010; 299(1-2): 15-8.
- [39] Dong, Y., N. Venketasubramanian, B.P. Chan, V.K. Sharma, M.J. Slavin, S.L. Collinson, P. Sachdev, Y.H. Chan, and C.L. Chen. Brief screening tests during acute admission in patients with mild stroke are predictive of vascular cognitive impairment 3-6 months after stroke. J Neurol Neurosurg Psychiatry 2012; 83(6): 580-5.
- [40] Wallin, A., A. Nordlund, M. Jonsson, K. Blennow, H. Zetterberg, A. Ohrfelt, J. Stalhammar, M. Eckerstrom, M. Carlsson, E. Olsson, M. Gothlin, J. Svensson, S. Rolstad, C. Eckerstrom, and M. Bjerke. Alzheimer's disease--subcortical vascular disease spectrum in a hospital-based setting: Overview of results from the Gothenburg MCI and dementia studies. J Cereb Blood Flow Metab 2016; 36(1): 95-113.
- [41] Hosseini, A.A., D. Meng, R.J. Simpson, and D.P. Auer. Mesiotemporal atrophy and hippocampal diffusivity distinguish amnestic from non-amnestic vascular cognitive impairment. Eur J Neurol 2017.
- [42] Yew, B., D.A. Nation, and I. for the Alzheimer's Disease Neuroimaging. Cerebrovascular resistance: effects on cognitive decline, cortical atrophy, and progression to dementia. Brain 2017.
- [43] Chao, L.L., S.T. Buckley, J. Kornak, N. Schuff, C. Madison, K. Yaffe, B.L. Miller, J.H. Kramer, and M.W. Weiner. ASL perfusion MRI predicts cognitive decline and conversion from MCI to dementia. Alzheimer Dis Assoc Disord 2010; 24(1): 19-27.
- [44] Grau-Olivares, M., A. Arboix, C. Junque, E.M. Arenaza-Urquijo, M. Rovira, and D. Bartres-Faz. Progressive gray matter atrophy in lacunar patients with vascular mild cognitive impairment. Cerebrovasc Dis 2010; 30(2): 157-66.
- [45] Nestor, S.M., B. Misic, J. Ramirez, J. Zhao, S.J. Graham, N. Verhoeff, D.T. Stuss, M. Masellis, and S.E. Black. Small vessel disease is linked to disrupted structural network covariance in Alzheimer's disease. Alzheimers Dement 2017; 13(7): 749-760.
- [46] Skrobot, O.A., J. Attems, M. Esiri, T. Hortobagyi, J.W. Ironside, R.N. Kalaria, A. King, G.A. Lammie, D. Mann, J. Neal, Y. Ben-Shlomo, P.G. Kehoe, and S. Love. Vascular cognitive impairment neuropathology guidelines (VCING): the contribution of cerebrovascular pathology to cognitive impairment. Brain 2016.
- [47] Hainsworth, A.H., S.M. Allan, J. Boltze, C. Cunningham, C. Farris, E. Head, M. Ihara, J.D. Isaacs, R.N. Kalaria, S.A. Lesnik Oberstein, M.B. Moss, B. Nitzsche, G.A. Rosenberg, J.W. Rutten, M. Salkovic-Petrisic, and A.M. Troen. Translational models for vascular cognitive impairment: a review including larger species. BMC Med 2017; 15(1): 16.
- [48] Lanza, G., P. Bramanti, M. Cantone, M. Pennisi, G. Pennisi, and R. Bella. Vascular Cognitive Impairment through the Looking Glass of Transcranial Magnetic Stimulation. Behav Neurol 2017; 2017: 1421326.
- [49] Bordet, R., R. Ihl, A.D. Korczyn, G. Lanza, J. Jansa, R. Hoerr, and A. Guekht. Towards the concept of disease-modifier in post-stroke or vascular cognitive impairment: a consensus report. BMC Med 2017; 15(1): 107.
- [50] Yue, N.C., A.M. Arnold, W.T. Longstreth, Jr., A.D. Elster, C.A. Jungreis, D.H. O'Leary, V.C. Poirier, and R.N. Bryan. Sulcal, ventricular, and white matter changes at MR imaging in the aging brain: data from the cardiovascular health study. Radiology 1997; 202(1): 33-9.

- [51] Scheltens, P., D. Leys, F. Barkhof, D. Huglo, H.C. Weinstein, P. Vermersch, M. Kuiper, M. Steinling, E.C. Wolters, and J. Valk. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry 1992; 55(10): 967-72.
- [52] Wahlund, L.O., F. Barkhof, F. Fazekas, L. Bronge, M. Augustin, M. Sjogren, A. Wallin, H. Ader, D. Leys, L. Pantoni, F. Pasquier, T. Erkinjuntti, P. Scheltens, and C. European Task Force on Age-Related White Matter. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001; 32(6): 1318-22.
- [53] Talairach J, Tournoux P. Co-Planar Sterotaxic Atlas of the Human Brain: 3-Dimensional Proportional System an Approach to Cerebral Imaging. New York: Thieme Medical Publishers; 1988.
- [54] Frisoni, G.B., C. Geroldi, A. Beltramello, A. Bianchetti, G. Binetti, G. Bordiga, C. DeCarli, M.P. Laakso, H. Soininen, C. Testa, O. Zanetti, and M. Trabucchi. Radial width of the temporal horn: a sensitive measure in Alzheimer disease. AJNR Am J Neuroradiol 2002; 23(1): 35-47.

Legends

Figure 1: Revised conceptualisation of VCI in VICCCS. Subtypes of VCI are divided according to level of VCI impairment into Mild VCI and Major VCI (VaD). Mild VCI is not further sub-divided at this time. Major VCI (VaD) is classified into 4 main subtypes as depicted. The 6 month temporal basis (denoted by the hashed box) for cognitive decline after stroke differentiates PSD from other forms of major VCI (VaD). Post stroke dementia (PSD) and Mixed dementias are further delineated if a comorbid neuropathology is present (N.B. AD and Dementia with Lewy bodies (DLB) are given as examples, with # denoting other possible combinations). Subcortical ischaemic vascular dementia or Multi-infarct (cortical) dementia subtype cases with these specific types of dementia alone, however cases also presenting with any other neurodegenerative pathology would then be categorised as Mixed dementias (dashed arrows) according to the comorbidities present.

Key words: vascular cognitive impairment, vascular dementia, guidelines, criteria, consensus, Delphi

Abbreviations:

Alzheimer's disease (AD)

Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC)

Instrumental activities of daily living / activities of daily living (IADL/ADL)

The American heart association/American stroke association (AHA/ASA)

Cerebrovascular disease (CVD)

Dementia with Lewy bodies (DLB)

Diagnostic and Statistical Manual of Mental Disorders (DSM)

International Statistical Classification of Diseases, 10th Revision (ICD-10)

Mild cognitive impairment (MCI)

Multi-infarct dementia (MID)

The National Institute of Neurological Disorders and Stroke–Association Internationale pour la

Recherche et l'Enseignement en Neurosciences (NINDS-AIREN)

National Institute of Neurological Disorders-Canadian Stroke Network (NINDS-CSN)

Post-stroke dementia (PSD)

Subcortical ischaemic vascular dementia (SIVaD)

Vascular dementia (VaD)

The International Society of Vascular Behavioural and Cognitive Disorders (VASCOG)

Vascular cognitive disorders (VCD)

Vascular cognitive impairment (VCI)

The Vascular Impairment of Cognition Classification Consensus Study (VICCCS)