Vascular Impairment of Cognition Classification Consensus Study (VICCCS)

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Abstract

Background: The variability in clinical manifestations of cognitive impairment caused by heterogeneous cerebrovascular disease and pathologies, collectively termed Vascular Cognitive Impairment (VCI), provides a challenge to clinical diagnosis and research. Numerous diagnostic criteria and research guidelines have been proposed for vascular dementia (VaD) and VCI, but as yet none is universally accepted. The different criteria are not readily comparable, which has implications for prevalence estimates, clinical diagnosis and treatment, interpretation and sharing of data.

Methods: The Vascular Impairment of Cognition Classification Consensus Study (VICCCS) has brought together a large pool of international participants from several disciplines. An extensive literature review of VCI identified prospective contributors, who were invited to participate in an online iterative consensus study using the Delphi approach. The initial 367 participants were asked to review concepts proposed in developing previous guidelines, leading, over six rounds to the development of a broader consensus of VCI, associated terminology and key research priorities.

Findings: With a mean of 122 (range 98-153) respondents over the course of the study, VICCCS provided overwhelming support for a broader conceptualisation of VCI, building on and clarifying concepts proposed by O'Brien and colleagues in 2003 that were strongly recommended for future use.

Interpretation: The VICCCS reflect a broad consensus of the guiding principles and agreed definitions for a revised conceptualisation of VCI, intended to facilitate standardisation in research and clinical interpretation and description of VCI.

Introduction

There is strong evidence that cerebrovascular pathology, including microinfarcts, lacunar infarcts, silent infarcts and white matter lesions, is moderately to strongly associated with cognitive decline[1-4]. Risk factors include hypertension, diabetes mellitus, smoking, atrial fibrillation, positive family history, age and hypercholesterolaemia[5-7], with possible increased risk due to *APOE* (epsilon 4 allele) and *MTHFR* variants[8]. Since Hachinski et al[9] proposed the term multi-infarct dementia, there have been numerous subsequent proposals to change the terminology and classification to try to capture the clinical and aetiological complexity of cognitive impairment caused by heterogeneous cerebrovascular disease and pathologies (Figure 1). These include: vascular dementia (VaD), vascular cognitive impairment (VCI), subcortical (ischaemic) vascular dementia and vascular cognitive disorder, which have given rise to multiple criteria and research guidelines[10-13] that are not readily interchangeable[14,15]. Thus it is not surprising that prevalence estimates vary widely in the literature, as do descriptions of clinical manifestations. However, VaD, being restricted to a severe form in the continuum of VCI, is probably the second commonest form of dementia after

Alzheimer's disease (AD), with an estimated prevalence of 16%, although as populations age this is likely to increase[10-12,16]. Cerebrovascular disease is also relatively common in other forms of dementia, including AD[17,18], and there is need to intensify research into possible pathological relationships. Research into causes and treatments of AD has progressed more than that for VaD and VCI, partly as a result of agreement on diagnostic criteria although these continue to evolve[19].

The lack of consensus criteria for diagnosis of VaD and VCI has impeded sharing and comparison of data on a larger scale and there has been widespread recognition of the need for greater harmony of approach within the research community[15,20]. A workgroup convened by the NINDS-CSN made progress in this regard[21], producing detailed research recommendations relating to procedures and assessment tools for VCI. However, their subsequent use seems to have been limited as evidenced by citations in research studies, and the receptiveness towards the wider adoption of these recommendations remains unclear.

The vascular impairment of cognition classification consensus study (VICCCS) was designed to achieve a broad consensus on the conceptualisation of impairment in cognition contributed to by vascular pathology, for clinical diagnosis and research. The aim was to agree a set of criteria that could be widely adopted within the field, to underpin future research. VICCCS has built on a large body of previous work to inform the way forward, with input from a broad spectrum of participants from across the community.

Methodology

Participant selection

Previous attempts to develop consensus criteria were largely based on comparatively smaller pools of opinion leaders as part of organised meetings, conferences or symposia[21]. Participants for the VICCCS were identified through unbiased review of published journal articles relating to the concept or diagnosis of VaD/VCI in Pubmed, up to August 2010. The intention for VICCCS was to draw upon the expertise of as many participants from as wide an array of disciplines as possible. Several relevant research networks, including British Association for Stroke Physicians, Alzheimer's Disease Neuroimaging Initiative (ADNI) and the European Alzheimer's Disease Consortium (EADC) were also invited.

The contact details were obtained for individuals identified by literature review (Figure 2a). To broaden the participant pool, those individuals were invited to provide details of interested colleagues. The 789 invitations initially sent generated an initial potential international multi-disciplinary participant pool of 367 participants, an endorsement of the project by the scientific community. Unlike in the previous endeavours, we used internet-based

survey forms in VICCCS to facilitate involvement of more participants and to allow them all to contribute with anonymity and parity. The project required considerable knowledge of relevant clinical and research aspects, and commitment of time to complete multiple rounds of surveys. Nonetheless, on average 122 participants contributed to each round (range 98-153) (Figure 2a). Of these, a mean of 72% (range 66-76%) were clinicians with direct involvement in clinical decision-making. The remainder were non-clinical researchers. Figure 2b depicts the continental distribution and research interests of the participant pool.

The VICCCS Delphi process

We used a Delphi approach, an iterative structured process involving a series of questionnaires with progressive refinement of questions to achieve acceptable levels of consensus amongst respondents[22]. Only the independent moderator (OS, who did not herself participate in the survey) had access to identification details of the respondents. The anonymity of responses facilitated free expression of opinion throughout the study. Controlled feedback of responses after each round, by the moderator, informed the nature of subsequent questions, allowing unbiased evolution of group judgements that may be difficult face-to-face. We adopted a threshold of two-thirds agreement to represent substantial consensus[23] for issues that had been refined through multiple iterative rounds. Six rounds of web-based surveys were administered, approximately one every 2 months, to maintain engagement. In the first two rounds, opinion was canvassed on published criteria, their utility and weaknesses. The remaining 4 rounds focused on addressing weaknesses and standardisation of terminology. A summary of the topics addressed in each round is provided as supplementary information.

Results

VICCCS Rounds 1 and 2: critical appraisal of preferred existing concepts and diagnostic assessment criteria
In the first round, views were also sought on the most important issues to be resolved. The extent of use of existing criteria and guidance, identified through literature review, were assessed. We separated questions on 'concept' papers (n=12), i.e. those concerning the scope and definition of VCI or its sub-types, from those proposing diagnostic criteria (n=15). Four papers covered both aspects and were included in both sections. Round 1 gathered participants' views on the scope and definitions, of these papers, but also invited additional suggestions for relevant manuscripts that should be considered. Participants were asked to indicate their familiarity with the papers and score their usefulness, from "*no longer relevant*" to "*useful in all cases*", and to select 3 concepts that could form the basis for wider acceptance. To reduce bias in selection that might have been caused by definitions that were older and perhaps more familiar, those selected that scored "*useful in most" or "useful in all cases"* were ranked to represent what was a 'considered useful vote'. The ranking showed that more recently published concepts, even if not widely known, were better regarded as a foundation for future use. The collated scores, including those on the utility of previously proposed definitions/criteria, were fed back to participants in Round 2. They were then asked to

reconsider all the concepts and to evaluate the criteria for diagnosis, including those that might be less familiar, before again ranking the criteria, after which low-ranking criteria would be eliminated from further consideration.

Almost 60% of respondents ranked the VCI construct of O'Brien and colleagues in 2003[24], representing a broad continuum from mild impairment to dementia, as the preferred conceptual basis. The second and third ranked definitions, which obtained 11% and 7% first-preference votes, also encompassed VCI and associated concepts (Figure 1).

In addition, 78% of respondents felt that the definition of VCI needed to be broader in scope than was currently the case. Therefore, the remaining VICCCS rounds focused on obtaining consensus on a revised conceptual model for VCI. The content of the subsequent rounds was based on suggestions by participants in response to the early-round questions on definition, scope, sensitivity to subtypes of VCI, clinical utility and likely level of adoption.

Rounds 3 – 6: formulation of a revised VCI concept

Although the constructs of O'Brien *et al* and those ranking nearest to this were widely supported, most respondents thought these needed refinement and elaboration. Questions concentrating on what modifications were necessary formed the basis of Round 3, and subsequent rounds were aimed at achieving consensus. In Round 3, we asked participants to state their agreement or disagreement with proposed general guiding principles for refinement of the concept of VCI. These had over 94% agreement; amendments proposed by some participants were reported for comment in Round 4. Consensus guiding principles are listed in Box 1.

Round 3 addressed *three areas* identified in Round 2 as meriting clarification or modification. While 29% of respondents thought the O'Brien construct did not need any major improvement, a percentage of respondents felt changes were desirable to its *scope* (13%), *sensitivity to subtypes* (31%) and *descriptiveness* (39%). The subsequent rounds worked towards improving these perceived limitations. A summary of proposed improvements are presented below. Clearly, 42% of respondents also thought that the O'Brien construct was not well aligned with clinical operational criteria. These limitations were subsequently addressed in a more focussed separate project (VICCCS *diagnosis*) on the development of operational criteria reported in full separately (however, see Box 3 and supplementary text for some reported findings).

Scope

Approximately one third (34%) of Round 3 participants suggested that other potential mechanisms of VCI should be included in the revised concept. In Round 4 participants were asked to vote on inclusion of the suggested mechanisms. There was a consensus that the additional mechanisms listed in Table 1 should be included within the revised concept of VCI. Over Rounds 4-6, there was also agreement as to what should constitute the arteriopathies subgroup (proposed in the O'Brien construct), as detailed in Table 2. In the VICCCS, specific arteriopathies are a descriptive term of cause rather than a subgroup of VCI (see Table 2).

<u>*Sensitivity to subtypes*</u>

The proposed subtypes of the revised concept of VCI according the VICCCS are depicted in Figure 3.

The O'Brien construct was thought by 31% of respondents to have limitations in the capture of subtypes of VCI. Whilst it acknowledged rare hereditary disorders that caused VCI, the construct focused mainly on sporadic forms of VCI. 78% of VICCCS participants suggested that both hereditary (i.e. "Type I" or "familial" VCI) and sporadic (i.e. "Type II" or "sporadic" VCI) should be encompassed within VCI. In Round 4, most (85%) respondents preferred the terms *sporadic* and *familial* to be used as *descriptive information* for various forms of VCI rather than to define separate categories.

Mild and Major VCI (VaD)

In the O'Brien construct, VaD was used as an umbrella term for subgroups of severe forms of VCI, such as hypoperfusion dementia and multi-infarct dementia. In Round 3 we asked whether the term VaD was still useful. No clear consensus emerged, although a small majority (56%) favoured its continued use. However, the timing of this VICCCS round coincided with the drafting of the fifth addition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5), widely used by clinicians world-wide. The draft DSM-5 proposal was that VaD or major VCD[25] be shown in parentheses with the description "major neurocognitive impairment due to vascular disease" as a classification group in DSM-5 for severe forms of impairment heretofore referred to as VaD[26]. We therefore sought VICCCS participants' views on the use of the terms "Mild" and "Major" in relation to VCI. Although only 39% of Round 4 respondents had been aware that work to develop DSM-5 was underway, 71% agreed that the revised VCI concept should use the terms "Mild" and "Major" to align the VICCCS recommendations with DSM-5. In Round 5 a 71% majority supported the terminology "Mild forms of VCI" and "Major forms of VCI (VaD)".

Further sub-typing of Mild forms of VCI

Subtyping of Mild forms of VCI was addressed in rounds 3-6. Further detail of this is provided in the supplementary information. Most participants (68%) were in favour of specifying subtypes. However, in response to a separate question 63% thought that this separation lacked supporting evidence and was premature, and participants could

not agree which subtype option (see Box 2) should be used. The VICCCS propose that Mild VCI is not sub-typed at this time until research provides better justification.

Further sub-typing of the Major VCI (VaD) subgroup

In Round 3 respondents were asked to revisit the subtypes of dementia proposed by O'Brien and colleagues and decide which should be recognised as stand-alone subtypes in the VICCCS, in view of other consensus decisions that some terms were useful as descriptors but not to define specific categories of VCI. The inclusion of the O'Brien subtypes originally listed received variable levels (81-50%) of agreement to remain as a subgroup (Supplementary table 1). We also canvassed opinion to potential relevance of other subtypes proposed by participants, however none were supported by a majority of respondents (Supplementary table 1).

In Round 4 most participants agreed that the lack of consensus around sub-types might be overcome if it were possible to avoid mixing site, severity and mechanism in the VCI subtypes (94% of respondents). 96% supported an effort that would develop a more systematic step-wise approach towards sub-typing of patients based on new VICCCS proposed categories of Location, Aetiology, Domains (affected) and Severity, provisionally named "LEDS" criteria (i.e. **L**ocation a**E**tiology **D**omains **S**everity). With this in mind, participants were asked which of the O'Brien sub-types allowed for more mutually exclusive grouping of patients or might be considered better suited as *descriptive terms* for either the 'mechanism' or 'location' of damage. The sub-types; "Specific arteriopathies", "Haemorrhagic" and "Hypoperfusion" were not supported as new standalone sub-types (13-18%) and thus are recommended as descriptive terms of causal mechanisms in VCI. The remaining sub-type terms received variable support between rounds. Round 6 collected a definitive decision on the issue of sub-types, with terms that did not achieve majority (67%) support to be descriptors. "Subcortical ischaemic" (83%) and "Multi-infarct (cortical)" (74%) were supported as sub-types of Major VCI (VaD). As in earlier rounds, post-stroke dementia (PSD) was supported (73%) as a sub-group and 86% thought it also helpful for clinical diagnosis. In contrast, despite near threshold support (66%), for consistency "Strategic infarct dementia" will also be proposed as a descriptive term for VCI. Additional suggestions for standalone sub-types of VCI were also invited. None of these was supported as a sub-group but there was support for "Vasculitis" (69%) as a helpful descriptive term of cause (Supplementary table 1). The resultant VICCCS recommended sub-types and descriptive terms are presented in Table 2.

<u>*Descriptiveness - clear definitions*</u>

"Mixed dementias"

Mixed dementia and how it is generally defined in clinical practice and research were identified as needing elucidation from the earliest rounds. This was not covered in depth by O'Brien and colleagues. 97% of respondents favoured change to the traditional imprecise usage of the term mixed dementia. In the final Delphi Round, 95% of

respondents agreed with a proposed solution to the differences in opinion on the term "mixed dementia" (see more detail of discussions in the supplementary information). This was that the term should serve only as an "umbrella" term for a sub-type of Major VCI (VaD) under which all phenotypes present would be specified as separate additional sub-groups e.g. patients would be referred to as having VCI-AD, VCI-LBD etc. according to co-morbidities present. 81% of respondents also endorsed this approach for both research and clinical applications, whilst there was also consensus (68%) that the order of abbreviations should reflect the relative contributions of the co-morbidities (as far as practicable).

"Post-stroke dementia"

While there was consensus for the term "post-stroke dementia" (PSD) to be used in research (73%) and clinical (86%) contexts, there was no consensus (63%) on its definition. We tried to address this in later rounds and continued to do so in the VICCCS *diagnosis*. Related issues that were thought necessary to clarify PSD, including the presence or absence of evidence of cognitive impairment prior to stroke and the timeframes for the emergence of PSD, are detailed in supplementary information. VICCCS consensus (78%) views on delineation of PSD are detailed in Box 3 and Figure 3. Of note was the consensus that the temporal association between cognitive decline and stroke differentiates PSD from other forms of major VCI (VaD), i.e. cognitive impairment within 6 months of having a stroke would be the determining factor for a diagnosis of PSD.

Consensus proposed definitions for Major VCI (VaD) subtypes (Post-stroke dementia, Mixed dementias, Subcortical ischaemic vascular dementia, Multi-infarct dementia) are presented in Box 3.

Discussion

The VICCCS has provided revision and consensus-based elaboration of the construct of VCI in the majority of areas addressed. A continued lack of consensus in some areas was mainly due to the lack of research data available at the time (for example, the sub-categorisation of Mild forms of VCI). The surveys showed that although half of the participants wanted to lessen the over-emphasis on memory-impairment in the conceptualisation of VCI, two-thirds acknowledged the benefit in the amnestic separation to allow alignment with current formats used for AD and MCI. Therefore, it was decided that no subtypes would be supported until research provides better justification.

Definition of more homogeneous groups was supported for Major VCI. These are important in the design of clinical trials. In addition, VICCCS has proposed in mixed dementias and PSD that all phenotypes present should be specified in more detail that defines additional sub-groups, i.e. patients would be referred to as having VCI-AD, VCI-LBD, or PSD-AD, PSD-LBD etc. according to the co-morbidities present, wherein the order of abbreviations reflected the perceived relative contributions of the co-morbidities. The development of approaches to improve the practicalities and accuracy of this would be important aspects of any future operational diagnostic protocols, whilst ongoing

research in biomarkers might serve to support this in time. Recent evidence does lend weight to this approach, showing that subcortical vascular dementia can be identified in an outpatient memory clinic setting, exhibiting partly different neuropsychological features and CSF-biochemical markers from those of AD[27]. Box 4 summarises this and other areas for future research either proposed or reflected in responses from the VICCCS.

VICCCS was conducted between 2010 and 2013 that coincided with the development of DSM-5[28] and VASCOG criteria for vascular cognitive disorders (VCD)[25]. VICCCS participants were given the opportunity to provide collective feedback on the draft DSM-5 proposals that were made available prior to its finalisation. This was enabled through a tailored survey developed (by OAS) in consultation with Professor Sachdev of the DSM-5 Neurocognitive Disorders Work Group and was prompted by request by the DSM-5 workgroup for input from the clinical research community into the process of refining the criteria. Yet, the level of awareness amongst the VICCCS participants of this request was relatively modest, pointing to a likely need for wider advertisement of such consultations in future. The VICCCS participants agreed that the *Minor* and *Major* terminologies proposed in DSM-5 were helpful and therefore should be adopted in VICCCS.

In relation to the subsequent published criteria (in 2014) for vascular cognitive disorders, VICCCS had previously explored (initial Delphi round, Figure 2) but was not supportive of the concept and the use of the term vascular cognitive disorder[12,29]. However, the VASCOG criteria are also reported to be aligned to DSM-5[25]. Comparisons between the diagnostic criteria are provided in a separate VICCCS *diagnosis* paper.

Considerations of the Delphi process on VICCCS outcomes

A key principle of the Delphi method is that decisions from a structured specialist group of individuals are more accurate. The use of online surveys in VICCCS, without the constraints usually imposed by a physical meeting, has facilitated the inclusion of an unprecedented large number of international participants who have enriched the discussions. The anonymity offered by this approach reduced the potential for any individuals to dominate direction of discussions. Furthermore, in combination with the repeated group feedback, the anonymity allowed contemplation and review of initial judgments and gave participants an opportunity to change their opinions without losing face, all of which contributed positively towards the generation of consensus[22,30]. The use of specific published papers helped to focus the discussion points and in some cases, increased awareness of previous studies, leading to more-informed decision making. After the initial rounds, structured, mostly closed questions were mainly employed that did minimise the scope for open feedback; however, the opportunity to provide comments or other answers were provided in primary discussion of topics. This sometimes increased the duration of the study and complexity of the arguments, such as in the discussion of mixed dementias and post-stroke dementia. This type of extended debate is useful but carries a risk of participant attrition, and variation in number of respondents in each round does,

of course, impact on the relative contribution of each respondent towards consensus. However, most topics were dealt with over a series of rounds giving multiple opportunities to confirm the consensus view. The maintenance of a high number of participants throughout the study provides assurance that a consensus concept of VCI has been realised.

Conclusions

VICCCS presents a new set of guidelines supported by a large International pool of clinical researchers. These guidelines have drawn upon and refined previous efforts to improve and clarify the conceptualisation of VCI. It is hoped that the VICCCS guidelines will be widely adopted in the VCI community and increase the levels of consistency and standardisation in the undertaking of VCI research. This in turn could significantly help with interpretation of findings across various studies and support the likelihood of more large-scale collaborative research that will be vital to help overcome historical limitations posed by the lower prevalence of VCI.

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