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Subcortical Vascular Cognitive Impairment staged through cdr's functional subsum (cdr-func): Preliminary results from an outpatient sample☆,☆☆

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ABSTRACT

Background: Staging vascular cognitive impairment (VCI) might be useful for sample selection in clinical trials and for guiding clinical decision-making. Clinical dementia rating (CDR) has been applied for staging cognitive impairments of different etiologies, but it may underestimate severity of non-Alzheimer's disease cognitive deficits.
Methods: Out of a total of 147 elderly subjects, 23 (mean age: 72.95 ± 7.51 years; 56% female; mean schooling: 9.52 ± 5.11 years) fulfilled clinical and neuroimaging criteria for VCI. Correlations among cognitive and functional status and scores in CDR and its subsums (CDR Sum of Boxes – CDR-SoB - and CDR Functional Subsum – CDR-FUNC) were performed.
Results: Both CDR-SoB and CDR-FUNC correlated with global cognitive performance, functional status, CLOX 2, working memory and abstraction tests. CDR global score only correlated with functional status.
Discussion: CDR-FUNC, as well as CDR-SoB, appear to be better indexes of severity in VCI than CDR global score.

1. Background

The observation that subcortical Vascular Cognitive Impairment (VCI) might progress insidiously from a presymptomatic high-risk state ("brain-at-risk") to Vascular Dementia (VaD) suggested that a continuum of growing severity of cognitive impairment exist within this clinical entity [1]. In Brazil, the prevalence of VaD in population-based studies varied considerably and ranged from 9.3 to 15.9%. Prevalence of VCI is probably higher, but it has not been established yet [2,3]. Staging cognitive impairment is useful for the appropriate selection of participants with similar levels of disease severity in clinical trials, as well as for guiding medical practitioners in clinical decision-making [4]. The Clinical Dementia Rating scale (CDR), proposed by Hughes et al. [5], is one of the most widely used measures for assessing the severity of cognitive and functional impairments associated with Alzheimer's disease (AD). Its global score results from an algorithm based on the clinician's impressions about the patient's Memory, Orientation, Problem Solving Capacity, Community Affairs, Home and Hobbies Management and Self Care Capacity. According to the global score, patients might be rated as normal (CDR = 0), presenting questionable (CDR = 0.5), mild (CDR = 1), moderate (CDR = 2) or severe dementia (CDR = 3) [5].

Through the past decades, a number of modifications on the use and the scoring of the instrument were adopted by studies. It became accepted by some research groups that the CDR should be rated after a semi-structured interview with the patient and a significant informant [6]. However, further papers reported that this procedure might be difficult for clinical and large-scale research settings due to its duration of 45 to 60 min. In order to provide a more reliable scoring of the subject's cognitive status, the interview included a set of neuropsychological tests, such as free-recall, orientation, calculation and abstraction tasks. This fact might be in contrast with the original concept of the CDR, which was meant to be performed free from psychometric tests results

Acronyms: AD, Alzheimer disease; CDR, Clinical Dementia Rating; CDR-SoB, Clinical Dementia Rating — Sum of Boxes; CDR-FUNC, Clinical Dementia Rating — Functional Subsum; MMSE, Mini-Mental State Examination; CAMCOG, Cambridge Cognitive Examination; FAQ, Pfeffer's Functional Activities Questionnaire; TMT-A, Trail-Making Test Part A; TMT-B, Trail-Making test Part B; VaD, Vascular Dementia; VCI, Vascular Cognitive Impairment; VF, Verbal Fluency.

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[5]. In addition, some researchers claimed that the Clinical Dementia Rating Sum-of-Boxes (CDR-SoB) might be a simpler tool for staging dementia, as it does not require an algorithm to calculate the total score. Furthermore it could be treated as interval data in statistical analyses, whereas the global score is an ordinal variable by nature [7]. It has been suggested that CDR may be more sensitive than informant-based assessment in identifying a high risk for white-matter lesions [8]. In addition, one study demonstrated that CDR-SoB might be as efficient as assessment of hippocampal atrophy through neuroimaging in predicting the progression from Mild Cognitive Impairment (MCI) to dementia [9].

Although CDR has been largely applied in clinical trials to individuals suffering from cognitive impairments of different etiologies [10–12], the question remains as to whether it is also a valuable and easy administered instrument for staging dementia of non-AD origin. Since scores in Memory and Orientation account for one third of both CDR global and CDR-SoB rates, those tools might underestimate severity of cognitive impairment of cases in which those functions are spared until advanced stages, such as Frontotemporal Dementia (FTD) and VCI. To deal with this issue, an adaptation of the CDR was published for trials in FTD [13], but currently, no validated instrument for staging VCI is available in South American countries.

Considering the intimate relationships between executive function (EF) and functional status, as suggested in previous studies [14,15], the authors hypothesized that the CDR's functional subsum (CDR-FUNC) [16], comprising the sum of scores in Problem Solving, Community Affairs, Home and Hobbies and Self Care, might be more strongly correlated with EF performance than the original CDR total score. This cross-sectional study aims to evaluate whether CDR-FUNC is superior to CDR and CDR-SoB for the assessment of cognitive and functional impairments in subcortical VCI subjects. For this purpose, we compared correlations between CDR and CDR subsums with scores in EF tests in a sample with subcortical cognitive deficits.

2. Methods

2.1. Subjects

Out of a total of 147 elderly outpatients, consecutively evaluated between October 2008 and August 2015, 23 subjects (mean age: 72.95 ± 7.51 years; 56% female; mean schooling: 9.52 ± 5.11 years) were selected for this study. The detailed sample selection criteria for this study have previously been published [17].

2.2. Neuropsychological and functional assessment

Patients underwent EF assessment, which included: Trail-Making Test (TMT) parts A and B (time to complete, errors, ratio TMT B:A and difference TMT B-A) [18], semantic verbal fluency [19], CLOX parts 1 and 2 (direct scores and ratio CLOX 2:1) [20], Cambridge Cognitive Examination (CAMCOG) Working Memory and Abstraction subtests [21,22]. Working Memory was assessed through CAMCOG's items 159–160, corresponding to ability to count backwards from 20 to 1 and ability to subtract serial sevens backwards from 100. The ratio CLOX 2:1 was calculated in order to remove the influence of visuospatial praxis over the task and provide a more sensitive index for EF [23]. Global cognitive performance was evaluated through Mini-Mental State Examination (MMSE) [24] and CAMCOG. Functional status was quantified using Pfeffer's Functional Activities Questionnaire (FAQ) [25].

Subcortical VCI was diagnosed if the subject performed below 1.5 standard deviation (sd) in at least one neuropsychological test according to normative values [18–20,22,24,26], in addition to presenting severity of white-matter hyperintensities (WMH) compatible with cerebrovascular disease on brain neuroimaging (see next section). Individuals with history of stroke, transient ischemic attack or cortical infarction compatible with large-vessel disease were excluded.

As demonstrated by Chang et al., CDR may detect MCI subjects with WMH [27]. The CDR's global score was calculated based on the examiners' impressions about the patients' cognitive and functional abilities, as originally suggested by Hughes et al. [5]. The CDR's functional subsum (CDR-FUNC) was obtained through the sum of scores on Judgment/Problem Solving, Community Affairs, Home/Hobbies and Self-Care boxes, ranging from 0 to 12 points [16]. The CDR-SoB resulted from the sum of the individual boxes scores, including Memory and Orientation.

The instruments used were in conformity to the directions of the Consensus for VaD of the Scientific Department of Cognitive Neurology and Aging of the Brazilian Academy of Neurology [28,29], where only validated versions into Brazilian Portuguese were proposed. Additionally, other validated instruments disclosed after the publication of this Consensus were also included.

2.3. Neuroimaging

Participants underwent Magnetic-Resonance Imaging (MRI) of the brain on a 1.5 T GE Signa Horizon machine. A modified version of the Fazekas Scale (mF) was used to evaluate periventricular and deep subcortical WMH on FLAIR sequence images [30]. It is worthwhile to stress that the WMH are significantly higher in the prefrontal region compared to other brain regions in subcortical VCI cases. Additionally, regardless of where in the brain this WMH are located, they are associated with frontal hypometabolism and executive dysfunction [31]. De Leon's scale was used to assess hippocampal atrophy (HA) [32]. Both Fazekas and de Leon scales were scored by a trained radiologist (D.M.) and a neurologist (E.E.) blind to the clinical and cognitive data.

Patients presenting moderate and severe WMH were included in the study. De Leon's scale was used to exclude individuals with HA compatible with neurodegenerative disorders, thus the cut-off score of HA ≤ 1 was adopted as inclusion criteria for this study. Since depression might play a confounding effect over both cognitive and functional assessments, individuals with significant depressive symptoms, as demonstrated by Cornell Depression Scale >8, were excluded [33].

2.4. Statistical analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 20 for Windows. Correlations between mean scores in cognitive and functional measures and CDR and its subsums, were evaluated through Spearman's Rho. Statistical significance was set at 0.05.

2.5. Ethics

This study is a branch of a project on Vascular-related cognitive disorders, approved by the Ethics Committee of the Institute of Psychiatry, Federal University of Rio de Janeiro (CEP-IPUB-UFRJ), under protocol number 416.952. Informed consent was obtained from participants or from a legal responsible prior to enrolment.

3. Results

Sociodemographic features, CDR's global scores and number of participants with moderate (mF = 2) and severe (mF = 3) WMH in the sample are depicted in Table 1.

CDR's global score did not show significant correlations with cognitive performance in our sample. Only functional status, assessed with FAQ presented moderate-to-strong correlation with this measure (rho = 0.623, $p < 0.01$). CDR-SoB and CDR-FUNC significantly correlated with scores in MMSE, CAMCOG, FAQ, CLOX 2, Working Memory and Abstraction. With the exception of TMT, VF and CLOX 1, CDR-SoB and mainly CDR-FUNC showed moderate or strong correlations with cognitive and functional scores in subjects with VCI (Table 2).

Table 1
Sociodemographic aspects of the sample.

	Sociodemographic aspects	Range
Gender (M/F)	9/14	–
Age (years)	72.9 ± 7.5	60–90
Schooling (years)	9.5 ± 5.1	4–19
MMSE	26.3 ± 3.3	18–30
CDR (0/0.5/1/2/3)	4/16/2/1/0	–
CDR-SoB	2.2 ± 2.5	0–11
CDR-FUNC	1.1 ± 1.6	0–7
mF (moderate/severe)	9/14	–

M = male; F = female; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating; CDR-SoB = CDR Sum-of-boxes; CDR-FUNC = CDR Functional Subsum; mF = modified Fazekas Scale.

4. Discussion

The identification of different stages of subcortical VCI may allow the selection of samples with homogeneous clinical features in clinical trials and studies, which may result in more consistent findings. Moreover, therapeutic approaches may differ from subjects with VCI with varied levels of cognitive impairment. However, the best method to measure severity in VCI still needs to be established. Previous studies have classified VCI through the volume of WMH in neuroimaging [34]; however, evidence showed that associations between lesion load and cognitive performance might be inconsistent, which indicated the need for other methods for staging VCI [30]. Furthermore, other variables, such as the cognitive reserve and hippocampal integrity, might influence the performances in tests, which could result in a great variability of scores among participants with similar lesion load [35].

In the present study, a subsum of the CDR, including only the boxes related with functional status, was compared with the CDR total score and the CDR-SoB in a sample with subcortical VCI patients. CDR-FUNC showed moderate-to-strong correlations with global cognitive performances and scores in tests that measured visuoconstructional praxis, working memory and abstract thinking. Functional status significantly correlated with CDR-FUNC. The same relationships were found when scores in CDR-SoB were analyzed. On the other hand, the CDR global score correlated only with functional status.

Those findings may reflect the impact of Memory and Orientation over the CDR global score. Both functions are highly dependent on the hippocampal integrity, as suggested by previous studies [36]. For this reason, CDR might underestimate the severity of the disease in subjects with cognitive impairment of non-AD etiology. In fact, we observed that some participants, who presented cognitive performances below normative values, exhibited CDR = 0. Not surprisingly, all of the three CDR measures correlated with functional status, since the instrument directly assesses capacity to perform basic and instrumental activities of daily living. Preliminary data suggests that detecting functional and decisional disabilities in VCI subjects may be facilitated by removing the effects of Memory and Orientation boxes over the CDR total score.

Table 2
Spearman's correlations between CDR, CDR-SoB and CDR-FUNC, and scores in cognitive and functional assessment.

	CDR	CDR-SoB	CDR-FUNC
MMSE	−0.314	−0.611**	−0.637**
CAMCOG	−0.270	−0.513*	−0.482*
FAQ	0.623**	0.655**	0.708**
TMT-A	0.188	0.225	0.103
ERRORS TMT-A	0.092	0.160	0.161
TMT-B	−0.058	0.168	0.200
ERRORS TMT-B	−0.155	0.035	0.029
TMT B:A	−0.192	0.122	0.271
TMT B-A	−0.062	0.223	0.265
VF	−0.065	−0.262	−0.250
CLOX 1	−0.167	−0.396	−0.359
CLOX 2	−0.318	−0.472*	−0.512*
CLOX 2:1	−0.124	−0.010	−0.111
WORKING MEMORY	−0.315	−0.494*	−0.436*
ABSTRACTION	−0.153	−0.436*	−0.449*

CDR = Clinical Dementia Rating; CDR-SoB = Clinical Dementia Rating- Sum of Boxes; CDR-FUNC = Clinical Dementia Rating – Functional Subsum; MMSE = Mini-Mental State Examination; CAMCOG = Cambridge Cognitive Examination; FAQ = Pfeffer's Functional Activities Questionnaire; TMT-A = Trail-Making Test Part A; TMT-B = Trail-Making test Part B; TMT B:A = Quotient TMT-B/TMT A; TMT B-A = Difference TMT B – TMT A; VF = Verbal Fluency.
* $p < 0.05$.
** $p < 0.01$.

Some other findings in this study should be furtherly discussed. CDR-SoB and CDR-FUNC significantly correlated with global cognitive performances, as measured by MMSE and CAMCOG. This result highlights the advantages of those measurements to detect overall cognitive functioning in comparison with CDR global score. Secondly, no correlation was identified among CDR-SoB or CDR-FUNC and the results in tests that assessed visual tracking and cognitive speed (TMT A), set shifting and inhibitory control (TMT B); semantic memory, working memory and cognitive speed (semantic VF), and planning and ideomotor praxis (CLOX 1). However, significant correlations were found between those CDR variants and visuoconstructional praxis (CLOX 2), CAMCOG's Working Memory and Abstraction subtests. The lack of correlation between CDR and its variants with results in most of the EF tests could be partially explained by the relative cognitive preservation of our sample. Indeed, the mean scores in the MMSE (26.39 ± 3.33) and the fact that 39.13% of the sample present only moderate volumes of vascular lesions indicate that most of the participants are mildly impaired. In this perspective, the finding that Abstraction correlated with CDR-SoB and CDR-FUNC in a sample with mild VCI is in line with a previous study from this group, in which CAMCOG's Abstraction task was the only test that distinguished early VCI subjects from controls [17]. Moreover, Visuoconstructive Praxis has shown to be impaired in subjects with moderate WMH, as reported by a systematic review [37]. Nordlund et al. [38] detected changes in Working Memory in Vascular Mild Cognitive Impairment, compared to controls and non-Vascular Mild Cognitive Impairment [38], but data on impairment of this function in early VCI appears to be controversial [37].

Some limitations of the present study ought to be commented. For instance, the lack of a gold standard battery to assess EF might result in divergent findings among studies, depending on the tests chosen to evaluate this function [39]. Moreover, the poor correlations between EF tests and CDR-FUNC may have been influenced by at least two aspects: Firstly, tasks deemed to assess specific aspects of EF, such as cognitive flexibility, working memory and planning may not be core measures of those processes, since they commonly require other EF and non-EF features. Especially in early stages of cognitive impairment, those functions act altogether and compensatory mechanisms may mitigate deficiencies in specific tasks, resulting in overall scores within the normal range in some tests. Secondly, some studies indicated that performance-based EF evaluation might present limited ecological validity, which may suggest that poor performances in tests might not correlate to functional difficulties in real-life [40]. Finally, this study included a small sample from a university outpatient setting. Larger population-based studies are necessary to confirm the present findings.

5. Conclusions

In this preliminary study, the authors disclosed a possible change in CDR's scoring system for subjects with VCI. This method might improve its accuracy to estimate severity in those individuals, which might be more associated with EF, praxis and functional impairments than with Memory and Orientation deficits. Staging VCI through CDR-FUNC might provide the identification of subjects with similar clinical features, independently of the WMH load, which might be useful in both clinical and research settings.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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