Hippocampal volume and CDR-SB can predict conversion to dementia in MCI patients

O volume do hipocampo e a soma dos subitens da escala CDR podem predizer a conversão para a demência nos pacientes com comprometimento cognitivo leve

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The most relevant challenge in dementia is the early identification of cases that would allow neuroprotective measures to delay or eventually prevent the onset of the illness. Mild cognitive impairment (MCI) and cognitive impairment no dementia (CIND) represent states of cognitive impairment, estimated by neuropsychological battery tests, with no sufficient criteria to meet the diagnosis of dementia. Despite the high rate of conversion to dementia, it is not know which patients will be demented. Several isolated variables have been evaluated as predictors of conversion but none has demonstrated good accuracy. The use of combined methods to better predict the risk of conversion is being developed in recent years.

The identification of predementia states can be done by clinical criteria or by semi-structured interviews, as the Clinical Dementia Rating (CDR). Its Global Score may be 0=normal, 0.5=questionable dementia (no dementia cognitive impairment), 1=mild dementia, 2=moderate dementia and 3=severe dementia. Individuals with CDR equal to 0.5 have annual conversion rate of 20%. The CDR sum of boxes scores (CDR-SB) may vary from 0 to 18 and enables a quantitative evaluation of impairment. In a five-year study, the annual conversion rates to CDR=1 (considered definite dementia) were 6.8% to CDR-SB=0, 10% to CDR-SB=0.5, 1 or 1.5 and 35.7% to CDR-SB=2, 2.5 or 3.

Objective: To evaluate the combination of two factors: clinical dementia rating sum of boxes scores (CDR-SB) and hippocampal volume (HV) as predictors of conversion from mild cognitive impairment (MCI) to dementia. Methods: Twenty-eight individuals (9 normal and 19 with MCI) were classified according to their CDR sum of boxes scores into 3 groups. Results: The hippocampal volume was significantly lower in the high-risk group and in those who developed dementia after two years. The rate of conversion was crescent among the three groups. Conclusion: We were proposed an additional measurement of the hippocampal volume which may be helpful in the prognosis. However, we noted that the CDR-SB is a method as efficient as neuroimaging to predict dementia with the advantage of being a procedure for low cost and easy implementation, more consistent with public policy.

Key words: geriatric psychiatry, neuroimage, mild cognitive impairment.

ABSTRACT

Objective: To evaluate the combination of two factors: clinical dementia rating sum of boxes scores (CDR-SB) and hippocampal volume (HV) as predictors of conversion from mild cognitive impairment (MCI) to dementia. Methods: Twenty-eight individuals (9 normal and 19 with MCI) were classified according to their CDR sum of boxes scores into 3 groups. Results: The hippocampal volume was significantly lower in the high-risk group and in those who developed dementia after two years. The rate of conversion was crescent among the three groups. Conclusion: We were proposed an additional measurement of the hippocampal volume which may be helpful in the prognosis. However, we noted that the CDR-SB is a method as efficient as neuroimaging to predict dementia with the advantage of being a procedure for low cost and easy implementation, more consistent with public policy.

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RESUMO

Objetivo: Avaliar a combinação de dois fatores: clinical dementia rating sum of boxes scores (CDR-SB) e volume hipocampal (VH) como preditores de conversão de ditúrbio cognitivo leve (DCL) em demência. Método: Vinte e oito indivíduos (9 normais e 19 com DCL) foram classificados de acordo com a soma dos escores CDR-SB em 3 grupos. Resultados: O volume do hipocampo foi significativamente menor no grupo de alto risco e naqueles que desenvolveram demência depois de dois anos. A taxa de conversão foi crescente entre os três grupos. Conclusão: Propusemos uma medição adicional do volume do hipocampo que pode ser útil no prognóstico. No entanto, notou-se que a CDR-SB é um método tão eficiente quanto neuroimagem para prever demência com a vantagem de ser um processo de baixo custo e de fácil implementação, mais consistente com a política pública.

Palavras-Chave: psiquiatria geriátrica, neuroimagem, distúrbio cognitivo leve.
Reduction in hippocampal volume (HV), measured by region of interest approach using magnetic resonance imaging (MRI), may be present in patients with MCI. Longitudinal studies measuring hippocampal atrophy indicate existence of a continuum from normal aging to MCI and dementia especially Alzheimer’s disease (AD). Such methodology has been used in a Brazilian setting already. Nowadays it is pointed as a predictor of conversion to dementia in MCI patients.

The objective of this study was to evaluate the combination of two factors: CDR-SB and HV as predictors of conversion from MCI to dementia.

**METHODS**

**Subjects**

The EPIDOSO study was the first community-based cohort study with elders in Brazil. It started in 1991, evaluating 1,667 individuals with 65 years and older, living in an urban district, in São Paulo city, whose main objective was to determine predictors of good health outcome. In 1998, 440 individuals, survivors from the original sample, began following up in the Centro de Estudos do Envelhecimento (CEE). Another study selected, among the CEE sample, those with Mini-Mental Status Examination (MMSE) less than 26 (n=108) and randomly assigned others 48 with MMSE ≥26. The 156 individuals entered a protocol that included CDR-SB, MMSE and Alzheimer’s disease assessment scale-cognitive subscale (ADAS-cog), which objective was to validate CDR for the diagnosis of dementia in Brazil. Among that sample, we selected only individuals who had no dementia at the initial evaluation (CDR=0 or 0.5), no formal indication to undergo MRI and had signed informed consent. Those were then divided into three groups, depending on their CDR-SB. Persons with CDR=0 (thus CDR-SB=0) were called “low-risk” group (LR), those with CDR=0.5 and CDR-SB=0.5, 1 or 1.5 were called “medium-risk” group (MR) and those with CDR=0.5 and CDR-SB=2, 2.5 or 3 were called “high-risk” group (HR).

**Procedures**

Individuals were submitted to brain MRI, within a maximum period of four months after the clinical and neuropsychological evaluation of the former study. Volumetric MRI scans were performed with a GE 1.5 Tesla Unit (Sigma System, General Electric Medical Systems, Milwaukee, Wisconsin) running version 5.4 software. Head position was standardized. A three-dimensional spoiled gradient recalled acquisition in the steady-state pulse sequence was used to obtain 124 contiguous images with slice thickness of 1.5 mm in the coronal plane for region-of-interest measures (echo time=5 milliseconds, repetition time=25 milliseconds, flip angle=40 degrees, acquisition matrix=256x192, number of excitations=1, field of vision=24 cm). After two years from the baseline, they were re-evaluated with CDR-SB, MMSE and ADAS-cog in order to detect clinical dementia (Global score of CDR=1). The imaging data were analyzed with Brains 2 software, which provides valid and reliable volume measurements of specific structures with a manually operated approach. Trained and reliable raters, blind to subject information, traced the hippocampus manually using valid protocols. All volumes were divided by intracranial volume.

All data were analyzed with the Statistical Package for the Social Sciences 13.0 for Windows (SPSS, Inc., Chicago, Illinois). The Mann-Whitney test was used for continuous data when comparing two groups and Kruskal-Wallis test for continuous data when comparing three or more groups. Association between the comparison groups and categorical variables was assessed with χ² test.

**RESULTS**

Twenty-eight individuals met the selection criteria. The proportion of women was 60.7%, mean age was 81±5.3 years and scholarship with mean 8±3.8 years. The distribution among the groups was: 9 LR, 11 MR and 8 HR. The three groups did not differ in their socio-demographic characteristics (Table 1).

No subject had clinical abnormalities on axial proton density and T2-weighted images. Subjects completed the scan without sedation or significant head movement. The HV was significantly smaller in HG, comparing to LR and MR (Kruskal-Wallis; p<0.001) (Table 1). After two years, no subject from LR, 4 (36.4%) subjects from MR and 7 (87.5%) from HR developed dementia (χ²; p<0.001). Dividing the sample into two groups, those who developed dementia (D-group) did not differ in gender, age and years of scholarship, compared to those who did not (ND-group) (Table 2). The D-group had mean HV smaller than the ND-group two years before the assessment (Mann Whitney; p=0.02).

### Table 1. Demographic characteristics and results of the three groups and of converters and non-converters.

|                       | Low-risk (n=9) | Medium-risk (n=11) | High-risk (n=8) | p-value  |
|-----------------------|---------------|--------------------|----------------|---------|
| Women/Men (% of women)| 6/3 (66)      | 5/6 (45)           | 6/2 (75)       | 0.38    |
| Age in years (mean±SD)| 81.0±5.0      | 80.0±4.8           | 82.5±6.6       | 0.45    |
| Years of scholarship (mean ± SD) | 8.2±3.5 | 8.0±4.4 | 7.6±3.7 | 0.92   |
| HV (% of ICV)         | 0.283±0.033   | 0.260±0.037        | 0.212±0.014    | <0.001 |

SD: standard deviation; HV: hippocampal volume; ICV: intracranial volume.
**DISCUSSION**

The HV was smaller in the HR group, suggesting a relationship between clinical performance and integrity of hippocampus. The individuals who developed dementia had smaller HV at baseline, supporting that it may be a predictor of conversion. Those results were expected and are supported by literature.

Although the main outcome, diagnosis of dementia, had not followed the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria, and was made without investigation of its causes. The criterion of CDR=1 is quite sufficient to diagnose dementia, with wide use in recent studies, as CDR=0.5 for CIND, and is a valid instrument in our setting.

Brain MRI has been more commonly requested by clinicians to identify causes of dementia, and CDR is already used in clinical practice in Brazil in order to dispense the anticholinesterasic medication. Thus, a simple modification in the standard evaluation of elders with cognitive complaints may be of great usefulness in predicting those that will convert to dementia. We propose an additional measurement of the hippocampal volume which may be helpful in the prognosis. However, we noted that the CDR-SB is a method as efficient as neuroimaging to predict dementia with the advantage of being a procedure for low cost and easy implementation, more consistent with public policy.

Further studies must evaluate the usefulness of this combination in larger samples and the plausibility of combining more biological markers as risk factors to improve the predictive power to identify those who will convert to dementia.

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