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

João Guilherme Fiorani Borgio[1,2], Leonardo Baldaçara[2], Walter dos Santos Moraes[1], Acioly L. T. Lacerda[2], Maria Beatriz Montaño[3], Andrea Parolin Jackowski[2], Sérgio Tufik[1], Luiz Roberto Ramos[3], Rodrigo Affonseca Bressan[2]

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.

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

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.

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[1]. 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[2]. The use of combined methods to better predict the risk of conversion is being developed in recent years[3,4].

The identification of predementia states can be done by clinical criteria[1] or by semi-structured interviews, as the Clinical Dementia Rating (CDR)[5]. 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[5]. Individuals with CDR equal to 0.5 have annual conversion rate of 20%[6]. 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[7].

Universidade Federal de São Paulo (UNIFESP), São Paulo SP, Brazil.

[1]Department of Psychobiology, UNIFESP, São Paulo SP, Brazil;

[2]Department of Psychiatry, UNIFESP, São Paulo SP, Brazil;

[3]Department of Preventive Medicine, UNIFESP, São Paulo SP, Brazil.

Correspondence: João Guilherme Fiorani Borgio; Rua Napoleão de Barros 925; 04024-002 São Paulo SP - Brasil; E-mail: joaoborgio@gmail.com

Conflict of interest: There is no conflict of interest to declare.

Received 17 May 2012; Received in final form 26 June 2012; Accepted 03 July 2012

Reduction in hippocampal volume (HV), measured by region of interest approach using magnetic resonance imaging (MRI), may be present in patients with MCI[8]. Longitudinal studies measuring hippocampal atrophy indicate existence of a continuum from normal aging to MCI and dementia specially Alzheimer's disease (AD)[9]. Such methodology has been used in a Brazilian setting already[10]. Nowadays it is pointed as a predictor of conversion to dementia in MCI patients[11].

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[12,13]. In 1998, 440 individuals, survivors from the original sample, begun 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)[14], which objective was to validate CDR for the diagnosis of dementia in Brazil[15]. Among that sample, we selected only individuals who had no dementia at the initial evaluation (CDR=0 or 0.5), no formal counter indication to underwent 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[15]. 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[16]. 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[17]. Trained and reliable raters, blind to subject information, traced the hippocampus manually using valid protocols[18]. 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 χ^2 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 (χ^2; 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.

Table 2. Demographic characteristics and results of converters and non-converters.

	No-dementia (n=17)	Dementia (n=11)	p-value
Women/Men (% of women)	11/6 (65)	6/5 (54)	0.59
Age in years (mean±SD)	80.8±4.8	81.3±6.3	0.62
Years of scholarship (mean±SD)	7.9±3.8	8.0±4.0	0.83
HV (% of ICV)	0.266±0.038	0.239±0.039	0.02

SD: standard deviation; HV: hippocampal volume; ICV: Intracranial volume.

DISCUSSION

The HV was smaller in the HR group, suggesting 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[19].

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[20], 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[21], as CDR=0.5 for CIND[22], and is a valid instrument in our setting[15,23].

Brain MRI has been more commonly requested by clinicians to identify causes of dementia[24], and CDR is already used in clinical practice in Brazil in order to dispense the anticholinesterasic medication[25]. 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.

References

1. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Inter Med 2004;256:183-194.
2. Boyle PA, Wilson RS, Aggarwal NT, Tang Y, Bennett DA. Mild cognitive impairment: risk of Alzheimer disease and rate of cognitive decline. Neurology 2006;67:441-445.
3. Visser PJ. Mild cognitive impairment. In: Pathy J, Sinclair AJ, Morley JE (ed.). Principles and practice of geriatric medicine. 4th ed. Hoboken: John Wiley & Sons, 2006. p. 1-7.
4. Borroni B, Premi E, Di Luca M, Padovani A. Combined biomarkers for early Alzheimer disease diagnosis. Curr Med Chem 2007;14:1171-1178.
5. Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology 1989;39:1159-1165.
6. Wang PN, Liu HC, Lin KN. The MCI study in Taiwan. Acta Neurol Taiwanica 2006;15:66-68.
7. Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH, et al. Mild cognitive impairment represents early-stage of Alzheimer disease. Arch Neurol 2001;58:397-405.
8. Jack CR Jr, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, et al. Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. Neurology 2000;55:484-489.
9. deToledo-Morrell L, Stoub TR, Bulgakova M, Wilson RS, Bennett DA, Leurgans S, et al. MRI-derived entorhinal volume is a good predictor of conversion from MCI to AD. Neurobiol Aging 2004;25:1197-1203.
10. Bottino CM, Castro CC, Gomes RL, Buchpiguel CA, Marchetti RL, Neto MR. Volumetric MRI measurements can differentiate Alzheimer's disease, mild cognitive impairment, and normal aging. Int Psychogeriatr 2002;14:59-72.
11. Devanand DP, Pradhaban G, Liu X, Khandji A, De Santi S, Segal S, et al. Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease. Neurology 2007;68:828-836.
12. Ramos LR, Toniolo J, Cendoroglo MS, et al. Two-year follow-up study of elderly residents in S. Paulo, Brazil: methodology and preliminary results. Rev Saude Publica 1998;32:397-407.
13. Ramos LR, Simoes EJ, Albert MS. Dependence in activities of daily living and cognitive impairment strongly predicted mortality in older urban residents in Brazil: a 2-year follow-up. J Am Geriatr Soc 2001;49:1168-1175.
14. Mohs RC, Cohen L. Alzheimer's Disease Assessment Scale (ADAS). Psychopharmacol Bull 1988;24:627-628.
15. Montaño MBMM, Ramos LR. Validade da versão em português da Clinical Dementia Rating. Rev Saude Pública 2005;39:912-917.
16. De Bellis MD, Hall J, Boring AM, Frustaci K, Moritz G. A pilot longitudinal study of hippocampal volumes in pediatric maltreatment-related posttraumatic stress disorder. Biol Psychiatry 2001;50:305-309.
17. Magnotta VA, Harris G, Andreasen NC, O'Leary DS, Yuh WT, Heckel D. Structural MR image processing using the BRAINS2 toolbox. Comput Med Imaging Graph 2002;26:251-264.
18. Schumann CM, Hamstra J, Goodlin-Jones BL, et al. The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. J Neurosci 2004;24:6392-6401.
19. Tapiola T, Pennanen C, Tapiola M, et al. MRI of hippocampus and entorhinal cortex in mild cognitive impairment: a follow-up study. Neurobiol Aging 2008;29:31-38.
20. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939-944.
21. Lim WS, Chin JJ, Lam CK, Lim PP, Sahadevan S. Clinical dementia rating: experience of a multi-racial Asian population. Alzheimer Dis Assoc Disord 2005;19:135-142.

22. Lynch CA, Walsh C, Blanco A, et al. The clinical dementia rating sum of box score in mild dementia. Dement Geriatr Cogn Disord 2006;21:40-43.

23. Maia AL, Godinho C, Ferreira ED, et al. Aplicação da versão brasileira da escala de avaliação clínica da demência (Clinical Dementia Rating – CDR) em amostras de pacientes com demência. Arq Neuropsiquiatr 2006;64:485-489.

24. van der Flier WM, Barkhof F, Scheltens P. Shifting paradigms in dementia: toward stratification of diagnosis and treatment using MRI. Ann N Y Acad Sci 2007;1097:215-224.

25. Beltrame A. Protocolos clínicos e diretrizes terapêuticas: medicamentos excepcionais. Brasília: Ministério da Saúde; 2002.