Arq Neuropsiquiatr 2007;65(4-B):1154-1157

SUBCLINICAL ENCEPHALOPATHY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Olga Maria Pinto de Lima[1,2], Ricardo de Oliveira-Souza[1,2], Omar da Rosa Santos[1], Pedro Araújo de Moraes[1], Leonardo Fontenelle de Sá[1], Osvaldo J.M. Nascimento[2]

ABSTRACT - *Background:* Clinical and experimental evidence suggests that chronic obstructive pulmonary disease (COPD) is associated with a variety of mental symptoms that range from cognitive slowing to mental confusion and dementia. *Purpose:* To test the hypothesis that COPD leads to cognitive impairment in the absence of acute confusion or dementia. *Method:* The global cognitive status of 30 patients with COPD without dementia or acute confusion and 34 controls was assessed with a Brazilian version of the Mini-Mental State Exam (MMSE). *Results:* The MMSE scores were significantly lower in the patient group and inversely related to the severity of COPD. This finding could not be attributed to age, education, gender, daytime sleepiness, hypoxemia, chronic tobacco use, or associated diseases such as diabetes, depression, high blood pressure or alcoholism. *Conclusion:* These results suggest the existence of a subclinical encephalopathy of COPD characterized by a subtle impairment of global cognitive ability.

KEY WORDS: chronic obstructive pulmonary disease, mini-mental state exam, subclinical encephalopathy.

Encefalopatia subclínica na doença pulmonar obstrutiva crônica

RESUMO - *Contexto:* Evidências clínicas e experimentais sugerem que a doença pulmonar obstrutiva crônica (DPOC) se associa a sintomas neurocomportamentais que variam da lentidão cognitiva à confusão mental e à demência. *Propósito:* Testar a hipótese de que a DPOC pode comprometer a cognição na ausência de estado confusional agudo ou de demência. *Método:* O estado cognitivo global de 30 pacientes com DPOC sem demência e sem confusão mental aguda e o de 34 controles foi examinado com a versão brasileira do Mini-Exame do Estado Mental (MEEM). *Resultados:* As pontuações no MEEM mostraram-se significativamente mais baixas nos pacientes, e inversamente relacionadas à gravidade da DPOC. Este achado não pôde ser atribuído a diferenças de idade, escolaridade, sonolência diurna, hypoxemia, tabagismo crônico, ou a doenças associadas como diabetes, depressão, hipertensão arterial ou alcoolismo. *Conclusão:* Estes resultados sugerem a existência de uma encefalopatia subclínica da DPOC caracterizada por comprometimento sutil da capacidade cognitiva global.

PALAVRAS-CHAVE: doença pulmonar obstrutiva crônica, mini-exame do estado mental, encefalopatia subclínica.

The neurological manifestations of hypercapnic respiratory disease were first described as a collection of manifestations consisting of headache, papilledema, fatigue, confusion and asterixis, eventually progressing to stupor and coma[1]. This clinical worsening is paralleled by a progressive slowing of the basic frequencies of the scalp electroencephalogram. Pathophysiologically the manifestations of hypercapnic respiratory disease reflect a progressive reduction of the alveolar surface of gas exchange, with respiratory acidosis and a concomitant retention of arterial CO_2. The critical role of CO_2 retention in the pathophysiology of headache and papilledema (the pseudotumor syndrome), as well as of muscle twitching, sleepiness and confusion (the syndrome of metabolic encephalopathy), is emphasized in the designation of this symptom-complex as "CO_2 narcosis"[2].

In contrast to what is usually observed in advanced or unstable chronic obstructive pulmonary disease (COPD), the cognitive status of clinically stable patients has been comparatively less studied. Because such patients are awake and oriented they may convey a cursory impression that they are cognitively intact. However, indirect evidence suggests that this may not be accurate, at least in some cases. Several reports indicate that a mild encephalopathy is a fairly common occurrence in hepatic, thyroid and renal disease[3-6]. Because these milder cognitive chang-

[1]Escola de Medicina e Cirurgia, Universidade Federal do Estado do Rio de Janeiro, Brazil; [2]Programa de Pós-Graduação em Neurologia e Neurociências da Universidade Federal Fluminense, Niterói RJ, Brazil.

Received 2 August 2007, received in final form 14 September 2007. Accepted 3 October 2007.

Dra. Olga Maria Pinto de Lima - Rua Antônio Basílio, 204 / 801 - 20511-190 Rio de Janeiro RJ - Brasil. E-mail: ompl@oi.com.br

es do not cross the diagnostic threshold for a formal diagnosis of acute confusional state or dementia[7], the expression "subclinical", or "subthreshold" encephalopathy has been employed as a shorthand reference. The subclinical encephalopathy of these conditions is characterized by mental slowing with a preserved global cognitive status. In particular, temporal and spatial orientation is, as a rule, entirely normal, yet some degree of cerebral impairment of a magnitude sufficient to compromise routine activities may still be detected by sensitive tests.

The aim of the present investigation was to test the hypothesis that clinically stable patients with COPD without overt cognitive symptoms may nevertheless present subtle cognitive impairments.

METHOD

Twenty men and 10 women with COPD and 34 controls (10 men and 24 women) without respiratory disease participated in the study as nonpaid volunteers after providing written informed consent. Between 2000 and 2006 patients with a clinical and spirometric diagnosis of COPD[8-10] were recruited from the outpatient sector of the Service of Respiratory and Lung Diseases of the Gaffrée e Guinle University Hospital (HUGG). They were clinically stable, normally engaged in their routine daily life activities, and had not been admitted to a hospital or treated with antibiotics in the preceding 30 days. These criteria selected only those patients who were in an optimal clinical condition during a relatively protracted period of stability, thus excluding patients with unstable disease. The control group was composed of hospital employees and acquaintances of the authors without a history or current clinical evidence of chronic respiratory disease. All medications currently in use, as well as red blood cell counts, blood glucose, blood urea nitrogen, blood pressure levels, and drinking habits were noted in each case. The study did not receive funding from research agencies and was conducted in the HUGG as part of the post-doctoral project of one of the authors (OMPL). The project was approved by Ethics Committee of the HUGG and the National Council of Education and Research (CONEPE).

Respiratory measures – The O_2 saturation (SaO_2) at rest, an index of alveolar gas exchange, was measured with a pulse oximeter immediately before the administration of the MMSE. COPD was staged according to individual FEV_1 values obtained after pharmacological bronchodilatation on the following 4-point ordinal scale: Stage 0: absence of disease; Stage 1: FEV_1>60%; Stage 2: 40% ≥ FEV_1 ≤60%; and Stage 3: FEV_1 <40%.

Cognitive, behavioral and socio-occupational measures – The Mini-Mental State Exam (MMSE) was used to gauge the global cognitive status as well as to ascertain that no participant was either demented or confused[11]. From 2003 to the present we adopted the official Brazilian version of the instrument[12]. Dementia, Acute Confusional State (Delirium) and Depression were diagnosed following the criteria of the American Psychiatric Association[13] and depression was additionally staged with the Beck Depression Inventory[14]. Daytime somnolence was assessed with the Epworth Sleepiness Scale[15]. Alcohol abuse was assessed with the CAGE questionnaire[16]. The cumulative cigarette consumption (number of cigarettes smoked during a lifetime) was estimated based on the number of smoking years and the yearly tobacco consumption. The overall socio-occupational level was assessed with the Global Assessment of Functioning (GAF) Scale[13].

Statistical analyses[17] – All results are expressed as means and standard deviations (x±sd). The significance of differences between means was assessed with analyses of variance (ANOVA). Associations between dimensional and categorical variables of interest were evaluated, respectively, with the Pearson correlation coefficient (r) and with the χ^2 test. A two-tailed critical value (α) of 0.05 was adopted as a significance threshold for all statistical tests. The effect size and statistical power of statistical tests of interest were calculated with G*Power[18].

RESULTS

The results are summarized in the Table. No significant differences were found between groups in relation to age (p>0.89), education (p>0.33), regular alcohol consumption (p>0.77), depression (p>0.07), and systolic (p>0.12) or diastolic (p>0.26) arterial blood pressure. However, there were more women among controls than among patients (p=0.01). As expected, there were more smokers in the patient group (p<0.001). The MMSE scores were significantly lower in patients than in controls (p<0.001) and inversely related to the severity of COPD (r= –0.49, p<0.001). Socio-occupational functioning was also inversely related to the severity of COPD (r= –0.47, p<0.001) and positively related to the MMSE scores (r=0.41, p<0.01). The statistical power (β) and effect size (d) of the mean difference between groups on MMSE performance were, respectively 0.95 ("high") and 0.74 ("medium to large").

DISCUSSION

The main findings of the present investigation can be summarized as follows: (i) patients with clinically stable COPD without dementia or acute confusion may nonetheless show global cognitive impairment, as revealed by comparatively lower scores on the MMSE, (ii) the MMSE was inversely related to the severity of COPD, and (iii) this cognitive impairment was not due to age, education, daytime sleepiness, hypoxemia, tobacco consumption, and associated diseases such as diabetes, depression, high blood pressure, and alcoholism.

Table. Demographic, clinical, and cognitive findings in patients with COPD and controls.

	Controls	COPD
Total N	34	30
Males	10	20
Females[1]	24	10
Age (in years)	66±8	65±8
Education (in years)	5.9±4.2	5.5±4.4
Diabetes	0	1
High blood pressure	15	11
Current systolic pressure	141±24	131±21
Current diastolic pressure	84±10	81±12
Drinks alcohol regularly	9	8
CAGE[2] (0-4)	0.30±0.70	0.33±0.76
History of tobacco smoking[1]	7	22
Age at start (in years)[1]	30±7	16±12
Cumulative cigarette consumption (cigarettes/life)[1]	81,565±194,019	455,793±284,140
SaO_2 (%)	—	95±2
FEV_1	—	42,1±15,9
Polycythemia	—	4
Hematocrit (%)	—	42,5±4,1
MMSE[1] (0-30)	28.1±1.9	26.0±3.5
Depression (DSM-IV)	3	7
Beck inventory (0-39)	7.1±5.9	10.5±8.3
Daytime sleepiness (0-24)	3	5
Epworth scale (0-24)	5.5±3.3	6.7±3.7
Global assessment of functioning[1] (0-100)	82±10	71±8

[1]p<0.005, two-tailed; [2]C ("Cutting down") A ("Annoyance") G ("Guilty") E ("Eye-openers").

These findings acquire additional relevance for the following reasons. Firstly, given the relatively low sensitivity of the MMSE, it is surprising that any differences in cognitive status between groups were noted at all. One implication of this finding is that the global cognitive level of our patients may in fact have been lower than it would be if they did not suffer from COPD. This decline is subtle and may easily pass unnoticed in routine consultations. Secondly, further studies are necessary to verify whether this relative decline has a direct adverse influence on daily life, because, if it does, cognitive status may be an independent target for treatment. Indirect evidence in favor of this possibility was the verification of significant associations between MMSE, COPD, and GAF scores.

Our study has several limitations that can be tackled in future research. The ease of administration of the MMSE is counterbalanced by its relative lack of sensibility and specificity. For example, studies addressing specific cognitive domains (such as executive performance, attention, cognitive speed) might give important clues on which cognitive processes best explain the performance of our patients on the MMSE. Some studies do indicate that patients with COPD present memory impairment, and this could explain at least in part the decline in the MMSE[19-25]. However, the different clinical characteristics of our patients and of the patients of the aforementioned studies preclude direct comparisons. Another limitation was the lack of arterial measures of $paCO_2$ and paO_2, which would allow more stringent conclusions on the mechanisms by which cognition fails in such cases.

Regardless the exact pathophysiological mechanisms at play our results support the proposal that a subclinical encephalopathy may indeed exist in at least a few cases of COPD. As far as we are aware, the concept of subclinical encephalopathy has not as yet been explicitly extended to COPD. The results of the present study, although admittedly preliminary, suggest that the concept of subclinical encephalopathy might be extended to patients with COPD. This idea would gain further support if such patients were

shown to perform slower than controls on measures of psychomotor speed, a hypothesis currently under study by our group.

Acknowledgments – The authors are indebted to Mr. Jorge Baçal and Mr. José Ricardo Pinheiro (Biblioteca do Instituto Osvaldo Cruz, RJ) for their kind support in finding the pertinent literature.

REFERENCES

1. Austen FK, Carmichael MW, Adams RD. Neurologic manifestations of chronic pulmonary insufficiency. N Eng J Med 1957;257:579-590.
2. Dulfano MJ, Ishikawa S. Hypercapnia: Mental changes and extrapulmonary complications. An expanded concept of the "CO_2 intoxication" syndrome. Ann Intern Med 1965;63:829-841.
3. Gilberstadt SJ, Gilberstadt H, Zieve L, Buegel B, Collier RO, McClain CJ. Psychomotor performance defects in cirrhotic patients without over encephalopathy. Arch Inten Med 1980;140:519-521.
4. Adams RD, Foley JM. The neurological disorder associated with liver disease. Res Publ Ass Res Nerv Ment Dis 1953;32:198-237.
5. Haggerty JJ Jr, Garbutt JC, Evans DL, et al. Subclinical hypothyroidism: a review of neuropsychiatric aspects. Int J Psychiatry Med 1990;20:193-208.
6. Figueiredo RB. Encefalopatia urêmica subclínica em pacientes hemodialisados. Comparação de diferentes testes neurocognitivos. Tese. Rio de Janeiro, 1998.
7. Plum F, Posner JB. The diagnosis of stupor and coma. 3.Ed. Philadelphia: FA Davis, 1980.
8. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. Am Rev Resp Dis 1983;127:725-734.
9. Barnes PJ. Chronic obstructive pulmonary disease. N Eng J Med 2000; 343:269-280.
10. Sociedade Brasileira de Pneumologia e Tisiologia. I Consenso Brasileiro de Doença Pulmonar Obstrutiva Crônica (DPOC). J Pneumol 2000;26 (Suppl 1):S4-S52.
11. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the mini-mental state examination by age and educational level. JAMA 1993;269:2386-2391.
12. Brucki MDS, Nitrini R, Caramelli P, Bertolucci PHF, Hokamoto IH. Sugestões para o uso do mini-exame do estado mental no Brasil. Arq Neuropsiquiatr 2003;61:777-781.
13. American Psychiatric Association. Diagnostic and Statistic Manual of Mental Disorders, 4.Ed. (DSM-IV). Washington, DC: American Psychiatric Association 1994.
14. Beck AT, Beck RW. Screening depression in family practice: a rapid technique. Postgrad Med 1972;52:81-85.
15. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-545.
16. Ewing JA. Detecting alcoholism: the CAGE questionnaire. J Am Med Ass 1984;252:1905-1907.
17. Motulsky H. Intuitive biostatistics. New York: Oxford Univ Press, 1995.
18. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods (in press).
19. Grant I, Heaton RK, McSweeny AJ, Adams KM, Timms RM. Neuropsychologic findings in hypoxemic chronic obstructive pulmonary disease. Arch Intern Med 1982;142:1970-1976.
20. Grant I, Prigatano GF, Heaton RK, McSweeny AJ, Wright EC, Adams KM. Progressive neuropsychologic impairment and hypoxemia. Arch Gen Psychiatry 1987;44:999-1006.
21. Prigatano GP, Parsons O, Wright E, Levib DC, Hawryluk G. Neuropsychological test performance in mildly hypoxemic patients with chronic obstructive pulmonary disease. J Consult Clin Psychol 1983;51:108-116.
22. Ozge C, Ozge A, Unai O. Cognitive and functional deterioration in patients with severe COPD. Behav Neurol 2006;17:121-130.
23. Heaton RK, Grant I, McSweeny AJ, Adams KM, Petty TL. Psychologic effects of continuous and nocturnal oxygen therapy in hypoxemic chronic obstructive pulmonary disease. Arch Intern Med 1983;142:1941-1947.
24. Incalzi RA, Corsonello A, Pedone C, et al. Drawing impairment predicts mortality in severe COPD. Chest 2006;130:1687-1694.
25. Huppert FA. Memory impairment associated with chronic hypoxia. J Neurol Neurosurg Psychiatry 1982;37;858-860.