

ALCOHOLISM AND SMOKING AS A RISK FACTOR FOR LATE-ONSET ALZHEIMER'S DISEASE: A META-ANALYSIS STUDY¹

ALCOOLISMO E TABAGISMO COMO FATOR DE RISCO PARA A OCORRÊNCIA TARDIA DA DOENÇA DE ALZHEIMER: ESTUDO DE META-ANÁLISE

Mauro José FONTELLES², Raimundo Miranda de CARVALHO³ and Marcelo Silveira D'OLIVEIRA⁴

RESUMO

Objective: to determine, using a systematic review of meta-analysis studies, whether or not, remote alcohol and smoke are significant risk factors for late-onset Alzheimer's disease. **Methods:** using a meta-analysis statistics model, 12 case-control studies (6 for alcohol /6 for smoke) published on Medline from 1984 until 1999 which evaluated the interaction between those factors and Alzheimer's disease were investigated. Mantel-Haenszel adjusted odds ratio (OR) and 95% confidence intervals were calculated in stratified data. Epi Info statistical software was used to determine p-value with significant level at 0.05. **Results:** the studies showed that a prior history of alcohol abuse wasn't associated with late-onset of dementia due to Alzheimer's disease (OR=0.98; 95%CI 0.63 to 1.52; and p-value=0.996). And the other studies showed that a prior history of tabagism wasn't considered as a risk factor for AD (OR=0.70; 95%CI 0.57 to 0.85; and p-value= 0.0004). **Conclusions:** In this study alcoholism wasn't considered as a risk factor for AD. On the other hand, in people who had the smoke habit, chances of late-onset Alzheimer's development were reduced in 30%. In that case, tabagism was considered as a protector factor for AD.

KEYWORDS: Alzheimer's disease, alcohol, smoke, risk factor, meta-analysis.

INTRODUCTION

In the literature, the Alzheimer's disease (AD) has been referred to as the main cause of dementia disorder in elderly patients and its etiology remains limited, inconsistent and controversial^{1,2}. On the other hand, there is an increasing interest in identify the reason for late occurrence of AD and many studies indicate that several kind of potential risk factors are involved, such as family history (dementia, mental retardation, Parkinson's disease), behaviors (smoking, alcohol abuse, coffee consumption, dietary habits), medical history (cancer, diabetes, hypertension, heart attack, head injury), life conditions (low level education, starvation/malnutrition) and others^{3,4,5}.

Although cigarette smoke and alcohol abuse have been reported as a potential risk factor for AD, the results from various case-control studies are inconclusive. Some show that smoking has a decrease in risk of AD,^{6,7,8} whereas others have found no association.^{9,10} On the other hand, alcohol abuse isn't pointed as a significant risk factor for some studies,^{7,9,10} even though it is still considered a potential risk factor for AD.^{3,4,5}

Thus, the purpose of this study was to determine, using a systematic review of meta-analysis studies, whether alcohol and tabagism are a significant risk factor for Alzheimer's disease.

Recebido em 03.01.2007 - Aprovado em 07.03.2007

¹Trabalho realizado no Departamento de Pesquisa, Divisão de Bioestatística, Universidade da Amazônia (UNAMA)

²TCBC – Doutor em Cirurgia do Trauma. Professor Titular da Disciplina de Anatomia Humana da Universidade da Amazônia – UNAMA. Professor do Curso de Pós-Graduação do Centro de Ciências Biológicas da UFPA. Cirurgião do Hospital de Pronto-Socorro Municipal de Belém.

³Graduando do Curso de Medicina da Universidade Federal do Pará (UFPA)

⁴Graduando do Curso de Medicina da Universidade do Estado do Pará (UEPA)

METHODS

Selection of studies

There are various studies in specialized literature showing the relationship between alcoholism and smoking, as a risk factor, and the farther occurrence of AD. Using a meta-analysis statistic model, the interaction between those factors and AD was investigated. This method of analysis involves three phases: identifying studies in specialized literature that are related to the topic to be analyzed; analyzing the results of the selected studies; integrating the results within a statistical model.

The use of meta-analysis in these cases is very efficient, as it not only aggregates the results of selected studies, but it also individually estimates the effect of each of them and tests the statistical significance of the total result of the studies in association.

In present research, 12 case-control studies were included and they were previously published on Medline from 1984 until 1999, investigating the association between these risk factors and the disease.

Statistical analysis

Analyses of two-by-two contingency table were performed. For each case-control study was estimated the association between prior alcohol abuse/ smoking and AD in terms of odds ratio and 95% confidence intervals (CI). Mantel-Haenszel adjusted odds ratio (OR) were calculated in stratified data. The Mantel-Haenszel method gives an estimate of the OR for each study when all the studies are jointly considered. Odd ratio calculation, according to the Mantel-Haenszel method, represents the ratio between the chance of an exposed group and a non-exposed group. If the chances are the same the OR will be 1, but if they are not, the OR calculation is a direct

manner, in relative terms, of showing the different chance (greater or smaller) for the exposed group.

This study considered exposure to alcohol and smoke, which meant that the OR was calculated by finding the ratio of chances of AD occurrence associated to alcoholism and tabagism with the chances of AD occurrence without a history of alcoholism and tabagism. Epi Info statistical software was used to determine p-value with a significant level at 5%.

RESULTS

After individually analyzing all the selected studies and reporting the relationship between alcohol and AD, it was observed that only one of the 6 evaluated studies had favorable effect regarding the association between alcoholism with AD occurrence. For doing so, alcohol wasn't considered as a significant risk factor. When the 6 studies were considered jointly, they didn't show a favorable statistical significance. The meta-analysis of the 6 studies showed that a history of alcoholism wasn't associated with dementia due to AD with OR estimated as 0.98 (95% CI 0.63 to 1.52 and p-value = 0.996). The results of meta-analysis for those studies are given in table 1. Figure 1 shows the individual and combined OR for the 6 studies.

Reporting the relationship between smoking and AD, it was observed that tabagism wasn't considered as a significant risk factor for late-onset Alzheimer's disease. When the 6 studies were considered jointly showed that smoking works as a protector factor for AD. The meta-analysis of the 6 studies showed that a history of smoking wasn't associated with dementia due to AD with OR estimated as 0.70 (95% CI 0.57 to 0.85 and p-value = 0.0004). The results of meta-analysis for those studies are given in table 2. Figure 2 shows the individual and combined OR for the 6 studies.

Table I –Odds ratio for the 6 case-control studies related to alcohol

Author	Year	N° of patients Case Control		Total	Odds Ratio	IC95%	P-value
<i>Shalat</i>	1987	6/98	14/162	20/250	0.69	0.23-2.01	0.460
<i>Barclay</i>	1989	34/39	36/39	70/78	0.57	0.10-3.03	0.458
<i>Graves</i>	1990	11/130	13/130	24/260	0.83	0.33-2.08	0.668
<i>Mendez</i>	1992	38/407	6/50	44/457	0.76	0.28-2.11	0.547
<i>Fratiglioni</i>	1993	8/98	7/266	15/364	3.29	1.05-10.42	0.018
<i>Harwood</i>	1999	11/580	5/286	16/866	1.09	0.35-3.62	0.878
<i>Combined</i>		108/1352	81/933	189/2275	0.98	0.63-1.52	0.996

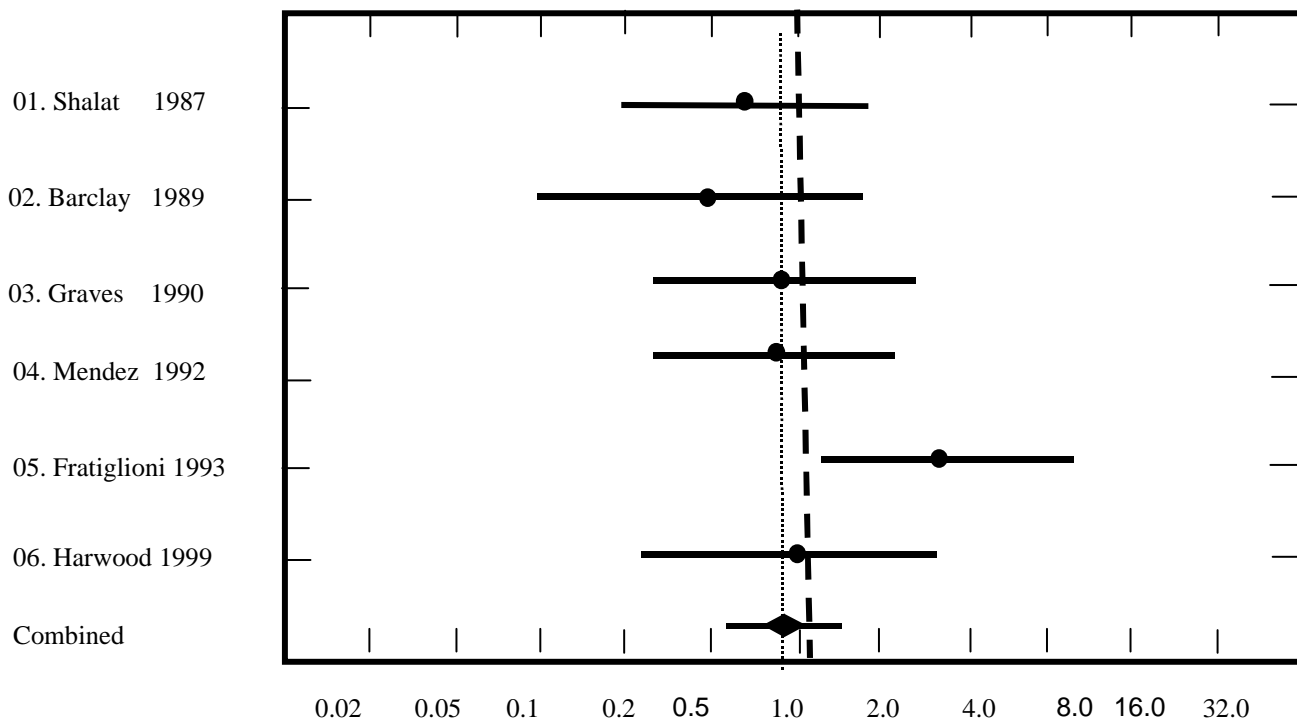


Figure 1. Odds ratio and IC95% for the six studies related to alcoholism used for meta-analysis

Table II - Odds ratio for the 6 case-control studies related to smoking

Author	Year	N° of patients		Total	Odds Ratio	IC95%	P-value
		Case	Control				
<i>Heyman</i>	1984	13/40	25/80	38/120	1.06	0.43-2.57	0.890
<i>Barclay</i>	1989	25/39	27/39	52/78	0.79	0.28-2.26	0.633
<i>Graves</i>	1990	67/130	76/130	143/260	0.76	0.45-1.27	0.262
<i>Van Duijin</i>	1991	89/193	102/195	191/388	0.78	0.51-1.19	0.223
<i>Prince</i>	1994	46/61	118/223	164/284	2.73	1.38-5.45	0.001
<i>Harwood</i>	1999	89/580	95/286	184/866	0.36	0.26-0.52	<0.0001
<i>Combined</i>		329/1013	443/953	772/1966	0.70	0.57-0.85	0.0004

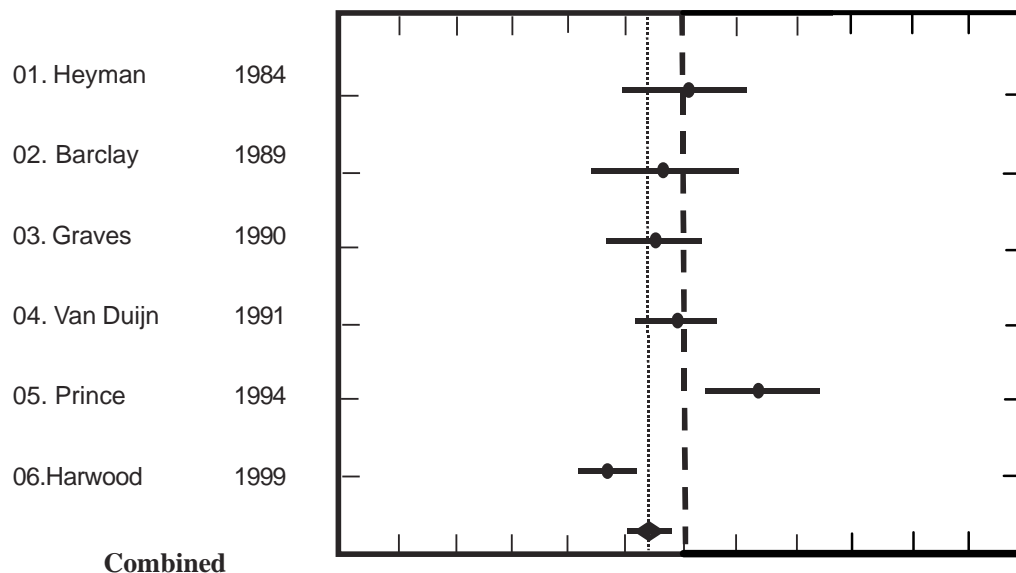


Figure 2. Odds ratio and IC95% for the six studies related to smoking used for meta-analysis.

DISCUSSION

Alzheimer's disease is the leading cause of dementia in elderly patients and it has an important impact over morbidity and mortality on these people.¹¹ The fact that the proportion of the population that is elderly remains increasing, especially in developed countries, just lead the scientific community to think about the increase of the frequency of AD,^{12,13} being advanced age a well-known risk factor.¹⁴ This disease is characterized as a heterogeneous disorder that may be caused by genetic or environmental risk factors or by a combination of both.^{15,16} In spite of lot of studies, the etiology of AD remains uncertain in the majority of cases,¹⁷ but it is clear that late-onset AD has a higher prevalence and incidence than early-onset AD.¹⁸

Pathologically, the illness is associated to the presence of several senile plaques and neurofibrillary tangles throughout the cerebral cortex. There are researches which revealed that the mistmetabolism of the β -amyloid precursor protein, such as aberrant processing or excessive production, is an essential event involved in the development of the pathology and maintenance of the disease process.¹⁷ The formation of these amyloid deposits is associated to a chronic activation of acute phase inflammatory process.^{17,19}

According to Tomlinson *et al*,²⁰ dementia is a symptom most commonly caused by Alzheimer's disease, accounting to 50 to 60% of the cases. For doing so, this disease needs to be studied in order to evaluate the influence of the risk factors that people are exposed to, such as tabagism and alcohol consumption.

Fratiglioni *et al*¹⁸ suggest that alcohol abuse might

play as an environmental factor for AD because they found an association between increased AD risk and high consumption of alcohol in their case-control study. This suggestion is controversial because there are several researches showing no association between alcoholism and increased risk for AD. Graves *et al*,⁸ using a meta-analysis statistics model, concluded that there was no significant association. Heyman *et al*⁹ and Graves *et al*²¹ had results that showed no association neither. Bachman *et al*²² had finds that suggest a decreased risk for AD by alcohol consumption. Nevertheless, there was no significant difference.

Tabagism is an important risk factor for Alzheimer's disease because it can affect central nervous system function.^{12,15} In the literature, there are many studies that investigated the relationship between smoking and AD, but there is a large variety of results. Heyman *et al*⁹ and Graves *et al*²¹ have not found significant difference in their researches. On the other hand, Shalat *et al*,²³ Launer *et al*,²⁴ and Prince *et al*²⁵ concluded tabagism has an increasing impact over the risk of AD, contradicting the finds of the present study. Ferris BG *et al*²⁶ considered that nicotine receptors may be desensitized by regular ingestion of nicotine contained in cigarettes, conducting to dementia's symptoms.

However, many researchers have showed, in their studies, an inverse association between smoking and development of Alzheimer's disease. Graves *et al*⁸ had statistical significance when analyzed this relation, while Broe *et al*⁷ found a small decrease in risk among patients exposed to this factor. Van Duijn *et al*,⁶ Jones *et al*,²⁷ and Grossberg *et al*²⁸ presented results that intensify the belief

on this inverse relationship.

The effect of smoking on the reduction of the AD risk is not clear, but some researchers try to explain it, considering actions caused by nicotine on the cerebral tissue.⁸ According to Whitehouse *et al*²⁹, patients with AD have a decrease in the number of nicotine receptors which is a pathological modification of the disease. Barclay *et al*¹¹ suggest that nicotine contained in cigarettes can compensate for the damage on the nicotinic receptors, postponing the development of the illness. Thus, it suggests that cholinergic abnormalities in AD may play a key role in pathogenesis of memory impairment and smoking habit may reflect changes in central nicotinic receptors. In addition, the smoking habit has been considered as a protective factor in others degenerative illnesses such as Parkinson's disease.³⁰

In this study, 12 case-control studies, previously published, investigated the risk for incident AD. Table 1 demonstrates that most of the analyzed studies presented negative results as for tendency to accept the association between alcoholism and increased risk of AD. In the same way, when all the studies were evaluated as a whole the result demonstrated that the total odds ratio was not favorable in relation to AD occurrence following alcoholism (OR = 0.98; p-value = 0.996). Table 2 shows that analyzed

studies, when evaluated together, demonstrated a protective effect in relation to AD development for those people exposed to smoking (OR = 0.70; p-value = 0.0004).

Although, the results obtained in part of the previous studies may be inconclusive or even contrary, when taken individually, meta-analysis is an appropriate method to be used, though those case-control studies are susceptible to recall bias which may explain the different results observed in relationship between alcohol/tabagism and this disease. Therefore, the risk factors should be studied further, even with new studies using meta-analysis with a more consistent and objective approach.

In summary, the results indicate that alcohol abuse is not related to AD and are consistent with the results of several previous case-control studies, while the relationship between AD and smoking was established in a protective way. Patients with a history of tabagism have a 30% smaller chance for late-onset Alzheimer's disease than those patients without this risk factor. But there is no consensus about it on the literature. For doing so, more studies are necessary in order to contribute to the knowledge about the influence of these risk factors on AD.

ACKNOWLEDGEMENTS

The authors would like to thank Mr. Edilson Silva Jr. for his helpful and review of the manuscript.

RESUMO

ALCOOLISMO E TABAGISMO COMO FATOR DE RISCO PARA A OCORRÊNCIA TARDIA DA DOENÇA DE ALZHEIMER: ESTUDO DE META-ANÁLISE

Mauro José FONTELLES, Raimundo Miranda de CARVALHO e Marcelo Silveira D'OLIVEIRA

Objetivo: estudar, em pacientes idosos, o uso de álcool e fumo como fatores de risco para a ocorrência tardia da doença de Alzheimer. **Método:** utilizando-se o modelo estatístico de meta-análise, os autores avaliaram 12 trabalhos científicos, sendo seis com alcoolismo e seis sobre tabagismo, todos do tipo caso-controle, previamente publicados pela MEDILINE, período de 1984 a 1999, os quais investigaram a associação entre estes fatores de risco e a doença. A odds ratio (OR) e o intervalo de confiança de 95% foram calculados segundo o método de Mantel-Haenszel. Os valores de p foram obtidos com o programa Epi Info, versão 6.04c. Considerou-se o nível alfa igual a 5%. **Resultados:** do total dos estudos avaliados, verificou-se que o uso de álcool, como fator de risco, não esteve associado ao desenvolvimento tardio da doença de Alzheimer (OR=0,98; IC95% 0,63-1,52 e p-valor=0,996). Porém, nestes pacientes, o tabagismo atuou como fator de proteção para a ocorrência da doença (OR=0,70; IC95% 0,57 a 0,85 e p-valor=0,0004). **Conclusão:** neste estudo, o alcoolismo não influenciou na ocorrência tardia da doença de Alzheimer. Por outro lado, em pacientes com história pregressa de tabagismo, a chance do aparecimento tardio da doença foi 30% menor quando comparada aos pacientes sem história clínica desse tipo de fator de risco, demonstrando ser o uso do fumo um fator de proteção para a doença em questão.

DESCRITORES: Doença de Alzheimer, álcool, fumo, fator de risco, meta-análise.

REFERENCES

1. HARWOOD, DG; BARKER, WW; LOEWENSTEIN, DA *et al* - A cross-ethnic analysis of risk factors for AD in white Hispanics and white non-Hispanics. *Neurology* 1999, 52(3): 551-6.
2. FLEMINGER, S; OLIVER, DL *et al* - Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. *J. Neurol. Neurosurg. Psychiatry* 2003, 74(7): 857-62.
3. SCHOFIELD, PW; TANG, M; MANDER, K *et al* - Alzheimer's disease after remote head injury: an incidence study. *J. Neurol. Neurosurg. Psychiatry* 1997, 62(2): 119-24.
4. MENDEZ, MF; UNDERWOOD, KL; ZANDER, BA *et al* - Risk factors of Alzheimer disease: a clinic pathologic study. *Neurology* 1992, 42(4):770-5.
5. BIDZAN, L; USSROWSKA, D - Risk factors for dementia of Alzheimer's type. *Psychiatria Polska* 1995, 29(suppl 3): 147-52.
6. VAN DUIJN, CM; HOFMAN, A - Relation between nicotine intake and Alzheimer's disease. *BMJ* 1991, 302: 1491-4.
7. BROE, GA; HENDERSON, AS; CREASEY, H *et al* - A case-control study of Alzheimer's disease in Australia. *Neurology* 1990, 40: 1698-707.
8. GRAVES, AB; VAN DUIJN, CM; CHANDRA, V *et al* - Alcohol and tobacco consumption as risk factors for Alzheimer's disease: a collaborative re-analysis of case-control studies. *Int. J. Epidemiol.* 1991, 20(suppl 2): 48-57.
9. HEYMAN, A; WILKINSON, WE; STAFFORD, JA *et al* - Alzheimer's Disease: a study of epidemiological aspects. *Ann. Neurol.* 1984, 15(4): 335-41.
10. AMADUCCI, LA; FRATIGLIONI, L; ROCCA, WA *et al* - Risk factors for clinically diagnosed Alzheimer's disease: a case-control study of an Italian population. *Neurology* 1986, 36: 922-31.
11. BARCLAY, L; KHEYFETS, S - Tobacco use in Alzheimer's disease. *Prog. Clin. Biol. Res.* 1989, 317: 189-94.
12. HEBERT, LE; SCHERR, PA; BECKETT, LA *et al* - Relation of smoking and alcohol consumption to incident Alzheimer's disease. *Am. J. Epidemiol.* 1992, 135(4): 347-55.
13. MEYER, JS; JUDD, BW; TAWAKLNA, T *et al* - Improved cognition after control of risk factors for multi-infarct dementia. *JAMA* 1986, 256(16): 2203-9.
14. KATZMAN, R; ARONSON, M; FULD, P *et al* - Development of dementing illnesses in an 80-year-old volunteer cohort. *Ann. Neurol.* 1989, 25(4): 317-24.
15. NICOLL, JAR; ROBERTS, GW; GRAHAM, DI - Amyloid beta-protein, APOE genotype and head injury. *Ann. NY Acad. Sci.* 1996, 777: 271-5.
16. MARSDEN, CD - Parkinson's disease. *Lancet* 1990, 1: 948-52.
17. GRAHAM, DI; GENTLEMAN, SM; NICOLL, JA *et al* - Is there a genetic basis for the deposition of beta-amyloid after fatal head injury? *Cell Mol. Neurobiol.* 1999, 19(1): 19-30.
18. FRATIGLIONI, L; AHLBOM, A; VIITANEN, M *et al* - Risk factors for late-onset Alzheimer's disease: a population-based, case-control study. *Ann. Neurol.* 1993, 33(3): 258-66.
19. GRAHAM, DI; GENTLEMAN, SM; LYNCH, A *et al* - Distribution of beta-amyloid protein in the brain following severe head injury. *Neuropathol. Appl. Neurobiol.* 1995, 21(1): 27-34.
20. TOMLINSON, BE; BLESSED, G; ROTH, M - Observations on the brains of demented old people. *J. Neurol. Sci.* 1970, 11: 205-42.
21. GRAVES, AB; WHITE, E; KOEPESELL, TD *et al* - A case-control study of Alzheimer's disease. *Ann. Neurol.* 1990, 28(6): 766-74.
22. BACHMAN, DL; GREEN, RC; BENKE, KS - Comparison of Alzheimer's disease risk factors in white and African American families. *Neurology* 2003, 60(8): 1372-4.
23. SHALAT, SL; SELTZER, B; PIDCOCK, C *et al* - Risk factors for Alzheimer's disease: a case-control study. *Neurology* 1987, 37(10): 1630-3.
24. LAUNER, LJ; ANDERSEN, K; DEWEY, ME *et al* - Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. *Neurology* 1999, 52(1): 78-84.
25. PRINCE, M; CULLEN, M; MANN, A - Risk factors for Alzheimer's disease and dementia: a case-control study based on the MRC elderly hypertension trial. *Neurology* 1994, 44(1): 97-104.
26. FERRIS, BG; SPEIZER, F; GAENSLEV, EA *et al* - Epidemiology standardization project. *Am. Rev. Respir. Dis.* 1978, 118: 21-2.
27. JONES, GM; SAHAKIAN, BJ; LEVY, R *et al* - Effects of acute subcutaneous nicotine on attention, information processing and short term memory in Alzheimer's disease. *Psychopharmacology* 1992, 108: 485-94.
28. GROSSBERG, GT; NAKRA, R; WOODWARD, V *et al* - Smoking as a risk factor for Alzheimer's disease. *J. Am. Geriatr. Soc.* 1989, 37: 822.
29. WHITEHOUSE PJ, MARTINO AM, WAGSTER MV *et al* - Reductions in [3H] nicotinic acetylcholine binding in Alzheimer's disease and Parkinson's disease: a autoradiographic study. *Neurology* 1988, 38: 720-3.

30. BARON, JA. Cigarette smoking and Parkinson's disease. *Neurology* 1986, 36: 1490-6.

Endereço para correspondência

Dr. Mauro José Fontelles. E-mail: mikefox@uol.com.br

Rua Antônio Barreto, 983/1502 – Umarizal

Belém – Pará.

CEP 66055-050

Fone: (91) 3225-1850