CARDIOVASCULAR RISK FACTORS AS POTENTIAL MARKERS FOR MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

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SUMMARY

Background: Mild cognitive impairment (MCI) is an early stage of cognitive decline that has a significant risk of converting to dementia. Cardiovascular pathology appears to have a major impact in cognitive decline, and it is clear that early identification and correction of cardiovascular morbidity could have a major impact on cognitive functioning.

Subjects and methods: Our study was conducted in order to identify some cardiovascular risk factors among patients with cognitive decline (MCI or Alzheimer disease-AD) and to find if there is any correlation with the degree of cognitive decline. We evaluated the body mass index, total cholesterol, hypertension, history of smoking, alcohol consumption and diabetes mellitus in patients with MCI and AD, compared with an age-matched control group.

Results: Regarding the body mass index, we observed a progressive decrease in patients with MCI and AD, in comparison with the control group. Similar aspects were also observed in the case of cholesterol levels, only that post hoc analysis revealed no significantly statistical differences between MCI and AD groups. The systolic blood pressure was increased in the patients with MCI and AD. Also, as in the case of cholesterol levels, post hoc analysis revealed no significantly statistical differences between MCI and AD groups. Pearson's correlation showed significant connections between the cardiovascular risk factors and the results of the cognitive evaluation.

Conclusions: Our results constitute additional evidence that cardiovascular risk factors are involved in cognitive regression. This finding could have an important impact on the management of dementia.

Key words: cardiovascular risk factors - mild cognitive impairment - Alzheimer's disease

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INTRODUCTION

Mild cognitive impairment (MCI) is an early stage of cognitive decline that has a significant risk of converting to dementia (Mariani et al. 2007). Alzheimer's disease (AD) and mild cognitive impairment have an increasing incidence in the elderly population. There is growing interest in identifying individuals who are not yet cognitively impaired, but are at a great risk for developing dementia, considering the fact that early dementia responds much better to treatment than when treatment is commenced only in the advanced stages of the illness.

Furthermore, it is generally believed that controlling vascular risk factors, such as hypertension, cholesterol, diabetes or smoking could have a major impact in preventing dementia (McCullagh et al. 2001, Purandare 2009, Maher et al. 2009). Different somatic modifications are believed to be involved in AD, such as the body mass index (BMI), together with some metabolic changes such as the cholesterol level or impaired glucose metabolism (Kivipelto et al. 2001, Fernández et al. 2008, Perry et al. 2003). However, the connection between these metabolic/somatic changes and cognitive deficits is not very clear.

In this way, cardiovascular pathology appears to have a major impact in cognitive decline and early identification and correction of cardiovascular morbidity could have a major protective impact on cognitive functioning.

The present study was conducted in order to identify some cardiovascular risk factors among patients with cognitive decline (MCI or AD) and to find out whether there is any correlation between these factors and the degree of cognitive deterioration. Thus, we evaluated several cardiovascular risk factors such as body mass index, cholesterol, hypertension, history of smoking, alcohol consumption and diabetes mellitus in patients with MCI and AD, compared with an age-matched control group.

SUBJECTS AND METHODS

Subjects

Our current study included 45 patients recruited from the Psychiatry University Hospital, Iasi, Romania. The subjects were classified into 3 groups: 15 patients formed the MCI group (5 females and 10 males; age: 63.2 years ± 4.2), 15 individuals were included in AD group (6 females and 9 males; age: 65.8 years ± 3.9)

and 15 were healthy age-matched controls (7 females and 8 males; age: 62.5 years ± 3.4).

The following exclusion criteria were used: 70 years old as a limit of age, no acute diseases and no recent stroke or heart attack. Cognitive and functional status was assed by Mini-Mental State Examination (Controls 26±0.5; MCI 22.2±0.3; AD 18.5±0.3) and Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) (Controls 7±0.2; MCI 14±0.4; AD 18.5±0.3) (Mohs et al. 1983, Padurariu et al. 2010). AD patients fulfilled the NINCDS ADRDA criteria (McKhan et al. 1984), whereas MCI diagnosis followed the criteria of Petersen et al. when there was evidence of memory impairment, preservation of general cognitive and functional abilities and absence of diagnosed dementia (Petersen et al. 1999). The cognitive testing was performed in the morning, basically between 10-12 a.m., while the patients were told not to consume any stimulants in the morning of the examination, such as coffee drinking or smoking. At the same time, the patients were clinically evaluated for cardiovascular risk factors such as: alcohol consumption (yes - for at least 100 ml/one day), smoking percent and diabetes mellitus. For BMI determination we divided weight, measured in kilograms by height, measured in meters squared. Blood pressure was measured in the right arm after participants had been seated for five minutes. However, blood samples were obtained in the morning before breakfast, allowed to clot and centrifuged immediately. Sera were aliquoted into Eppendorf tubes and stored at -80°C until determination of serum total cholesterol concentrations, which was performed in the hospital central laboratory (Kivipelto et al. 2001b, Fitzpatrick et al. 2009). AD patients were treated with anti-dementia dugs, such as donepezil and memantine, while the MCI patients were selected from the patients who presented to our clinic especially for memory complains and met the aforementioned Petersen criteria. Additionally, in all cases no other psychiatric illness was associated.

The study was conducted according to the provisions of the Helsinki Declaration and the local ethics committee approved the study. All the patients or their families signed the consent form for their participation in this study.

Statistical analysis

The results for the cardiovascular risk factors were analyzed using one-way analysis of variance (one-way ANOVA). Post hoc analyses were performed using Tukey's honestly significant difference test in order to compare the differences between MCI and AD groups. All results are expressed as mean ± SD. F values for which p<0.05 were regarded as statistically significant. Also, Pearson's correlation coefficient was used to evaluate the connection between the scores of the cognitive tests (MMSE and ADAS-Cog) and cardiovascular risk factors.

RESULTS

Regarding the body mass index, we observed a decrease in both patients with MCI and AD, in comparison with the control group (Figure 1). However, this decrease of BMI was statistically significant only in the case of the AD group (F(1,28)=14, p=0.001), while in the case of the MCI group the decrease was not significant, as compared to the control group (F(1,28)=3, p=0.11). Also, post hoc analysis revealed significantly statistical differences between MCI and AD groups (p=0.007).

The analysis of cholesterol revealed a significant decrease in both MCI (F(1,28)=13, p=0.001) and AD (F(1,28)=28, p<0.0001) groups, in comparison with the control group (Figure 2). However, post hoc analysis revealed no significantly statistical differences between MCI and AD groups (p=0.112).

The systolic blood pressure was increased in the patients with MCI (F(1,28)=15, p=0.0005) and AD (F(1,28)=22, p<0.0001), in comparison with the control group, as figure 3 shows. However, as in the case of cholesterol levels, post hoc analysis revealed no significantly statistical differences between MCI and AD groups (p=0.532).
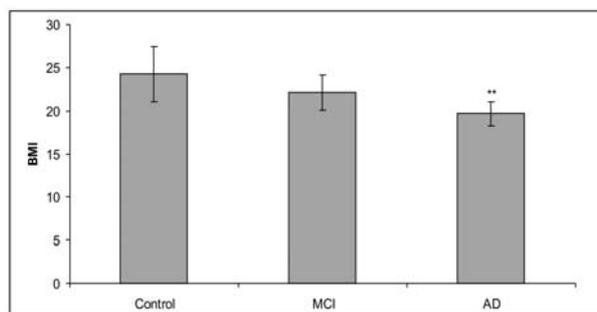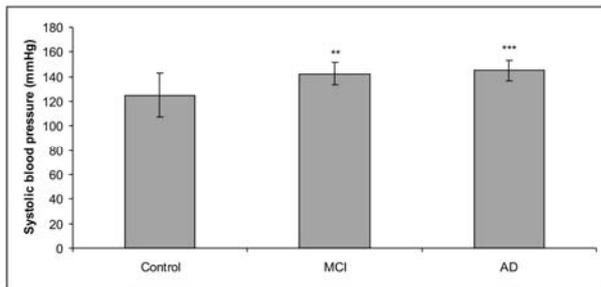

BMI values in control, MCI and AD patients. The values are mean ± SD. (n = 15 per group), **p =0.001 vs. control

Figure 1. BMI values in control, MCI and AD patients. The values are mean ± SD. (n=15 per group), **p=0.001 vs. control
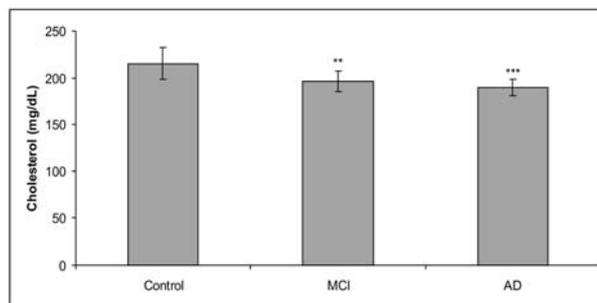
Total cholesterol concentrations in control, MCI and AD patients serum. The values are mean ± SD (n=15 per group), ** p=0.001, *** p<0.0001

Figure 2. Total cholesterol concentrations in control, MCI and AD patients serum. The values are mean ± SD (n=15 per group), ** p=0.001, *** p<0.0001.

Systolic blood pressure values in control, MCI and AD patients. The values are mean ± SD (n=15 per group), ** p=0.0005, *** p<0.0001

Figure 3. Systolic blood pressure values in control, MCI and AD patients. The values are mean ± SD (n=15 per group), ** p=00005, *** p<00001

Interestingly, when we determined the linear regression between the scores of the cognitive tests (MMSE and ADAS-Cog) and the aforementioned cardiovascular risk factors, we found significant correlations in all cases, as follows: BMI vs. MMSE (n=45, r=0.383, p=0.009); BMI vs. ADAS-Cog (n=45, r=-0.441, p=0.002); cholesterol vs. MMSE (n=45, r=0.635, p=0.0001); cholesterol vs. ADAS-Cog (n=45, r=-0.589, p=0.0001); systolic blood pressure vs. MMSE (n=45, r=-0.561, p=0.0001) and systolic blood pressure vs. ADAS-Cog (n=45, r=0.610, p=0.0001). These data suggest that the cognitive regression can be a result of the cardiovascular distress.

Additionally, the history of diabetes mellitus was recorded. An increased number of patients with diabetes mellitus were observed in AD (13.33%) and especially in the MCI group (26.66%), in comparison to controls (6.66%). Also, increased alcohol consumption percenttage was reported in AD patients (46.66 % as compared to controls – 26.66 %), while the smoking percent was identical in control and AD groups (60%), but reduced in MCI patients (33%).

DISCUSSION

In the present study, our main objective was to investigate some very common cardiovascular risk factors in MCI and AD patients, compared with an age-matched control group. Moreover, we wanted to analyze the correlations between the cardiovascular risk factors and the degree of cognitive impairment. Our results point to the general idea that cognitive regression can be the result of the cardiovascular distress.

It is believed that multiple causes are competing in the induction of dementia and lately there is growing evidence that cardiovascular risk factors interfere with normal cognitive functioning and could be involved in the etiopathogenesis of AD.

BMI is a statistical measurement commonly used to estimate the quantity of body fat. Obesity has been frequently associated with MCI and AD. Recent reports found that adiposity, measured by BMI could play an important role in cognitive decline, especially in AD (Whitmer et al. 2005, Goble 2005, Cronk et al. 2010, Chu et al. 2009).

However, there are also studies which demonstrated that a lower BMI could be associated with cognitive deficits, even years before the onset of dementia (Johnson et al. 2006). In consistence with these reports, our results also showed a decrease of BMI in both MCI and AD groups, compared to control group. There are not enough data to explain the real cause of this weight loss or the connection with cognitive compromise, but as we mentioned earlier, evidence shows that weight loss can occur before the diagnostic of dementia and this could be used as a predictor factor (Buchman et al. 2005, Hughes et al. 2009). Also, in our study, we observed a progressive decrease of BMI, as post hoc analysis revealed significantly statistical differences between MCI and AD groups. This data may suggest that after onset of dementia patients may experience a more severe decline at their weight levels.

Since the significance of a decreased adiposity in demented patients is not well understood, it can be assumed that it is the result of life-style changes which are known to occur in these subjects, due to poor nourishment or metabolism changes. Also, another cause may be that the brain areas involved in controlling weight, such as mesial temporal cortex, are the target of various insults in predemented patients (Grundman et al. 1996). Also, it is believed that a higher BMI index may offer brain protection in the elderly through increasing insulin-growth factor I, leptin and estrogen levels, which are correlated with a better cognitive functioning (Hughes et al. 2009). Some authors even suggested that a treatment for weight loss could be helpful in this matter (Luchsinger et al. 2007).

It seems that the complex relations between BMI and the cognitive functions could depend on the age of the individual, since it is only in late life (as in the case of our study) that it was found that a weight decline could represent a risk for cognitive impairment (Atti et al. 2008), while in midlife a higher BMI can be a risk factor for developing AD (Fitzpatrick et al. 2009). In this way, it seems that the predictive ability of BMI changes across time. Also, while our results showed a decrease of BMI in both MCI and AD groups in late-life patients, further aspects can be discussed regarding the possible cause of this weight loss. This could be due on the one hand to decreased intake. In this way, some previous studies tried to examine the intake levels in AD patients, but the results were contradictory (Bucht et al. 1990, Poehlman et al. 2000, Tamura et al. 2007). However, it seems that weight loss is correlated with decreased independence in self-feeding. This could be an important aspect, considering that AD symptoms include confusion, loss of memory, apraxia or anosmia (Poehlman et al. 2000). In this way, there are some very interesting studies describing various auditive and visual aspects which could influence the food intake in AD patients, such as the necessity of increased lighting (vs.

the decreased ability to see light colored foods in AD patients) and noise reduction, that could result in improved nutritional status (McDaniel et al. 2001). Also, it may be possible to increase food intake in AD patients by increasing the energy density of their food (Poehlman et al. 2000).

Additionally, some other comorbidities could explain this aspect. In fact, it is known that weight loss occurs with various comorbidities at older ages and this is often reflective of poor health (Fitzpatrick et al. 2009).

High total cholesterol is a common marker of cardiovascular and also cerebrovascular pathology, but its implication in AD and MCI is not well understood, since a high level of cholesterol was associated with both an increased and a decrease risk of dementia. Like in the case of BMI, these results could be explained by a different range of subject's age.

Interestingly, in late-life, a decreased level of serum cholesterol was demonstrated to have a positive correlation with cognitive regression (Solomon et al. 2007). It is known that the brain has a high concentration of cholesterol and disturbances in brain cholesterol metabolism may lead to pathological changes found in AD. There is also evidence that cholesterol began to decrease several years before the onset of dementia and this could be used as a marker for the risk of AD (Mielke et al. 2005). In our study, which used patients around 65 years old, we found that cognitive impaired subjects had a lower level of total cholesterol, compared to the control group and these levels of cholesterol are significantly correlated with the cognitive deficiencies, as showed by Pearson correlations. However other studies have been identifying cholesterol as a risk factor for AD and MCI when this is found in middle-age patients (Notkola et al. 1998, Kivipelto et al. 2002, Solomon et al. 2007).

In this way, our results could be explained merely by a decrease in the cholesterol intake, considering the recent studies which demonstrated that a 5% cholesterol-enriched diet for 5 months results in impaired learning and long-term memory in rats, as well a significantly reduction in the number of cholinergic neurons in the basal nucleus of Meynert/decreased acetylcholine levels in the cortex and increased levels of beta-amyloid (1-42) and tau protein (Ullrich et al. 2010, Puglielli et al. 2003, Refolo et al. 2001), rather then a coincident finding of dementia.

Another cardiovascular risk factor is hypertension, which was found to have a negative correlation with cognitive functions, especially with memory, attention and executive functions (Hanon 2005, Vicario 2005). Also, long-term high blood pressure interferes with brain perfusion leading to chronic ischemic lesions and silent strokes (Staessen et al. 1997, Ciobica et al. 2009), while some other studies revealed that hypertension can be also involved in amyloid β deposits or neurofibrillary tangles formation (Lee et al. 2003, Bomboi et al. 2010). Neuropathological findings regarding the effects of

chronic hypertension revealed severe atherosclerosis, ventricular enlargement, silent infarct, white matter lesions and brain atrophy, when compared to normotensive individuals (Esiri et al. 1999, Vermeer et al. 2003, Takeda et al. 2008, Nagai et al. 2010). These brain changes could determine cognitive regression which is often found in patients with chronic hypertension (Takeda et al. 2008, Ciobica et al. 2009). Moreover, many studies found that the reduction of systolic blood pressure may have a protective effect against cognitive impairment (Fogari et al. 2003, 2006).

In our study we also found an increased systolic blood pressure in both MCI and AD groups, compared to controls. Moreover, we found a significant correlation between the cognitive decline and systolic blood pressure, as showed by Pearson correlation. There are conflicting results regarding the connection between blood pressure and the cognitive decline, with studies showing that hypertension is a risk factor for dementia (Posner et al. 2002, Luchsinger et al. 2005), while some authors did not find any association or even a negative correlation with the cognitive decline (Qiu et al. 2003, Beeri et al. 2009). Also, there are some reports stating that the treatment of hypertension does not lower the risk of cognitive dysfunction (Hansson et al. 1999, Mielke et al. 2005). Anyway, it is always difficult to interpret the real signification of hypertension, since many other factors have to be taken into consideration, such as the cholesterol level, smoking status, cardiac diseases or disturbances of the glucose metabolism.

Regarding the implication of diabetes mellitus in dementia, there is clear evidence that glucose intolerance is associated with cognitive decline such as MCI and AD (Ott et al. 1999, Curb et al. 1999). In the present study we found that cognitive impaired patients (especially those with MCI) had a higher rate of diabetes mellitus than the control group. Also, some longitudinal studies found that diabetics have a double risk of cognitive decline, compared to non-diabetics and even a greater cognitive decline when associated with hypertension (Hassing et al. 2004).

Smoking status was also determined in this study. There are conflicting results regarding this subject, with a number of studies reporting an association between smoking and an accelerated risk for dementia (Meyer et al. 2000, Tyas et al. 2003, Aggarwal et al. 2006, Hritcu et al. 2009) and others failing to find any association between smoking and dementia (Kalmijn et al. 2000, Bowirrat et al. 2002, Bhargava et al. 2006). Also, in a comprehensive study regarding the conversion from MCI to dementia followed for an average of 3 years, risk factors associated with the probability of conversion included atrial fibrillation and low serum folate levels, but not smoking (Ravaglia et al. 2006, Swan et al. 2007). In our study, we reported a reduced smoking percent only in MCI patients, with no significant differences between AD and control groups. This could be explained by the facilitatory and neuroprotective (Mihailescu et al. 2000, Swan et al.

2007) effects of nicotine in some AD patients, mainly expressed by the nicotinic stimulation of the remaining population of cholinergic receptors and/or the modulation of the ascending catacholaminergic systems' activity, such as mesolimbic dopaminergic projections, as well as the "self-medication" hypothesis of smoking in various neuropsychiatric diseases (Mihailescu et al. 2000, Audrain-McGovern et al. 2009, Padurariu et al. 2010).

Also, regarding the alcohol consumption status, we found an increased alcohol consumption percent in the AD group and a reduced percent in MCI patients, compared to controls. There are also controversies regarding this aspect, but it is generally suggested that moderate alcohol consumption, especially in earlier adult life, is associated with a reduced risk of dementia (Ruitenberg et al. 2002, Peters et al. 2008). However, in our study we were only interested to know if the patients were chronic drinkers (at least 100 ml/one day) or not. Additionally, some very interesting studies have discussed the join effects of tobacco and alcohol consumption on risk of Alzheimer's disease, stating a protective effect of alcohol consumption, which is better expressed in non-smokers individuals (García et al. 2010).

Regarding our results, we reported an increase percentage of alcohol consumption in AD patients, which is quite unexpected considering that alcohol can worsen the neurological, cognitive and behavioral changes that people are experiencing in the early stages of Alzheimer disease. However, it is important to mention that sometimes alcohol has an important ritual or social role in the life of the person who has dementia (e.g. they always have a drink before dinner), giving the feeling of independence and control (Wiscott et al. 2001).

An important limitation of our study is represented by the small sample size.

CONCLUSIONS

Our results provide additional evidence that cardiovascular risk factors are involved in cognitive regression. Thus, the body mass index was progressively decreased in patients with MCI and AD, as were the cholesterol levels, but only that in this case no significant differences were seen between the MCI and AD groups. Additionally, the systolic blood pressure was increased in both groups with MCI and AD. More importantly, significant correlations were observed between the cardiovascular risk factors and the results of the cognitive evaluation. Moreover, these indices are simple to detect and could have a great potential as possible risk factors, which makes them easy targets in the prevention of dementia. However, further studies are necessary in order to determine their exact role in dementia progression. Also, studies regarding the association of multiple cardiovascular factors in dementia and how these factors correlates with each other seem to be warranted.

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