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Role of cardiovascular risk factors (CRF) in the patients with mild cognitive impairment (MCI)

E. Ettorre, E. Cerra, B. Marigliano, M. Vigliotta, A. Vulcano, C. Fossati, G. De Benedetto, A. Servello, P. Andreozzi, V. Marigliano *

Department of Cardiovascular, Respiratory, Nephrological and Geriatric Sciences "Sapienza" University of Rome, Umberto I, Policlinico di Roma. Viale del Policlinico 155, I-00161 Roma, Italy

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ABSTRACT

Few therapeutic options are available nowadays to improve the prognosis of patients with Alzheimer's disease (AD). There are rather several evidences in literature that controlling vascular risk factors may be an effective intervention for modifying the course of this disease. The aim of our study was to investigate the role of CRF in 50 patients with MCI according to Petersens's criteria, and to evaluate their influence on cognitive and behavioral features of the disease and on the development of dementia. Statistical analysis of the data showed that the 60% of the patients with MCI and CRF developed dementia, while 40% maintained the same cognitive conditions at the end of the study. Only 32% of the subjects without cardiovascular comorbidities developed dementia. The results of the study suggest that CRF play a key role in cognitive decline of patients with MCI. Patients with MCI and CRF showed not only worse cognitive performances, but also behavioral disorders, depression and functional disability. Patients with CRF had higher conversion rate to AD than the other group, with a mean disease-free period 3 months shorter than the control group.

1. Introduction

The latest epidemiological studies give an estimate of over 35 million people with AD in the world, delineating a real health emergency. It is therefore necessary to identify strategies for prevention and treatment of AD for delaying the onset of the disease at least to 5 years, indirectly reducing the number of new cases of 50% (Panza et al., 2008). In recent years, the main interest of scientific research has been to identify new modifiable risk factors and to develop new perspectives for the prevention and treatment of AD (Modrego et al., 2008; Helzner et al., 2009). Research has been especially focusing on the study of preclinical forms of dementia, including MCI, which is an intermediate clinical condition between normal aging and dementia. MCI is defined by an impairment of memory and other cognitive functions, not so serious as dementia (Weiner et al., 2008). More and more evidence suggests that the control of CRF may change the progression of the disease, in preclinical stages of cognitive impairment (Goldstein et al., 2008).

The aim of this study was to examine the possible role of CRF on clinical development of AD in a group of individuals diagnosed with MCI, giving an assessment of their capability to worsen cognitive impairment, behavioral disorders or to influence the transition from MCI to AD. The aim of this study was also to assess whether CRF, such as hypertension (Beeri et al., 2009), hyperlipidemia (Duron and Hanon, 2008), diabetes mellitus type 2 (Whitmer et al., 2009), tobacco smoking (Yaffe et al., 2009), carotid atheromasia (Villeneuve et al., 2009) could be considered predictive markers of faster conversion to dementia in MCI patients.

2. Subjects and methods

Our study included 50 subjects diagnosed with MCI who underwent a cognitive evaluation during year 2007 at AD Evaluation Unit of the Department of Aging, Policlinico Umberto I of Rome. Each patient underwent a general clinical evaluation and some instrumental checks (carotid ultrasound imaging, 12-lead standard electrocardiogram, blood laboratory analysis, dosage of thyroid hormones, dosage of vitamin B_{12} and folate, brain Magnetic Resonance Imaging study or Computed Tomography) in order to rule out a possible secondary cause of dementia and assess general clinical conditions of the subject. First level cognitive evaluation was performed on all the subjects using Mini Mental State Examination (MMSE), Geriatric Depression Scale (GDS), Neuropsychiatric Inventory (NPI), Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), Tinetti Scale. A second level cognitive assessment was later performed, with a

* Corresponding author. Tel.: +39 06 445 3600; fax: +39 06 445 6316.
E-mail address: evaristo.ettorre@uniroma1.it (V. Marigliano).

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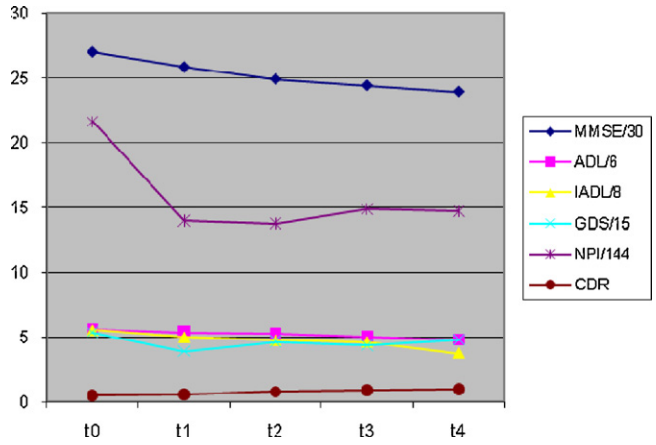

Fig. 1. Cognitive tests in Group 1.

comprehensive battery of neuropsycological tests for the study of all cognitive domains. Memory was assessed by immediate and delayed recall of Rey's 15 words Test, Memory for Prose test and the Recognition Figures Test. Attentional capacity was quantified by Attentional Numerical Matrices Test and Trail Making Test; Phonological and Categorical Verbal Fluency Test and Generation Phrases Test were administered in order to study lexical ability. We assessed praxic abilities by Copying Designs Test, Execution of Orders Test and Clock Drawing Test. We finally evaluated logical capabilities with Guest Verbal Test. Diagnosis of MCI was made by the diagnostic criteria of Petersen (Fig. 1).

Clinical Dementia Rating (CDR) scale was used to assess cognition as normal, MCI, mild, moderate or severe dementia (CDR respectively 0, 0.5, 1, 2, 3). All individuals with a diagnosis of cerebrovascular disease and other neurodegenerative diseases (stroke from 6 months before the onset of cognitive decline or diagnosis of Parkinson's disease in the year preceding the beginning of memory disorder) were excluded from the study. Each patient was reassessed after 6 months through the whole battery of cognitive tests scheduled by the research protocol. Dementia was diagnosed following the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), while for the nosographic diagnosis of AD were used the National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's disease and related Disorders Association criteria (NINCDS-ADRDA) (McKhann et al., 1984). The 50 selected subjects were finally divided into two groups: the first group made up of 25 patients, 17 females and 8 males, with a diagnosis of MCI and CRF (12 subjects with hypertension and other CRF, 13 patients with a diagnosis of hypertension and without other risk factors). The second group of 25 patients, 16 females and 9 males with a diagnosis of MCI without CRF (Table 1).

3. Results

All 50 patients enrolled in our study completed the programmed follow-up of 2 years. Statistical analysis of the data showed that 60% of MCI patients with CRF developed AD, while 40% of these patients maintained the same CDR until the end of follow-up time. Only 32% of controls (subjects without CRF) developed dementia. All patients underwent brain magnetic resonance imaging (MRI) or computed tomography (CT) at the beginning of the study: patients with CRF and patients of the control group who developed dementia showed pathological alterations of brain tissues like cortical atrophy sometimes associated to cortico-subcortical ischemic brain lesions, while patients of the control group without dementia at the end of follow up did not generally show the same pathological neuroimaging.

Table 1
Conversion times (months) in the 2 groups.

	Group 1	Group 2
	24	24
	24	24
	24	24
	24	24
	24	24
	24	24
	24	24
	24	24
	24	24
	24	24
	6	24
	6	24
	6	24
	6	24
	6	24
	12	24
	12	24
	12	24
	12	6
	12	6
	12	6
	18	12
	18	12
	24	18
Total mean	16.8	19.44

It is worth mentioning that we also found pathological alterations at brain neuroimaging in some patients with unchanged cognitive performances and without functional dysautonomia at the end of follow-up time. Figs. 1 and 2 show the scores that all patients obtained in first level cognitive tests. The analysis of these scores shows that the patients of Group 1 obtained mean scores of MMSE one point lower each control (from a T_0 value of 26.96 to 23.9 at the end of the study) and lower scores in ADL and IADL at the end of the follow-up time. The CDR has been increasing gradually till the end of follow-up time. The patients of Group 2 showed a slow decline of mean MMSE values during follow-up time, together with lower scores of ADL and IADL scales for decreased functional autonomy. On the contrary, GDS scores showed small variations with non-linear trend for the time of the study. Mean scores of NPI did not vary during observational time, showing a steady trend, while CDR scores increased during follow up time. CDR scores in Group 1 show that cognitive performances of 14 among 25 patients (60% of the sample) got worse, turning to dementia in 2 years, while in Group 2, only 8 patients among 25 (32% of the sample) converted from MCI to dementia. CDR trend looks different in the two groups, as the following figure shows. The mean CDR after 2 years of follow up resulted to be 0.96 in the

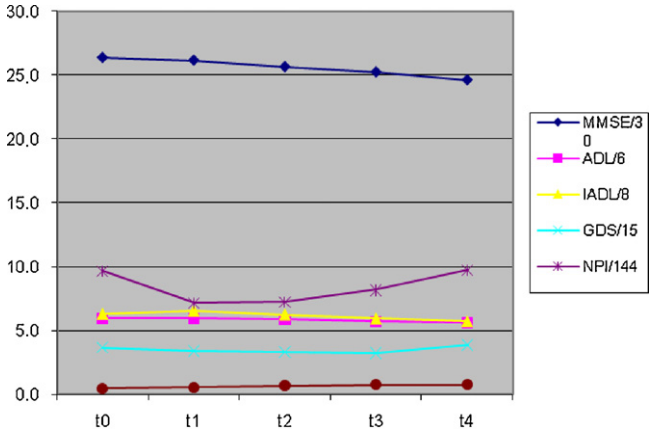

Fig. 2. Cognitive tests in Group 2.

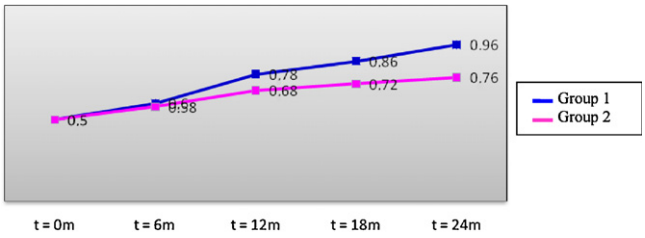

Fig. 3. Trend of CDR in the two groups.

first group and 0.76 in the second (variance 0.0354 and 0.01132, respectively) showing worse cognitive performances in the first group than in the second one. The trend of the mean values of CDR shows a greater tendency to conversion in the first group, as it can be seen in Fig. 3 showing the trend line of the two groups and the value of the slope. The trend of ADL and IADL scores shows a worsening of the basic functional activities during follow-up time, with higher mean values in the second group. IADL scores show a descending trend in both groups, as indicating an increasing disability in instrumental activities of daily living. The comparison of GDS scores in the two groups showed lower values, with a linear trend, in patients without CRF compared to MCI patients with CRF. Analyzing the NPI score we can find an average difference between the trend of the two groups of 11.9 (21.6 Group 1 – 9.7 Group 2) at $t = 0$, while at the end of follow up ($t = 4$) the average difference drops to 4.92 (from 14.68 to 9.76). It is interesting to note a different conversion time in the two groups: group 1 has an average conversion time of 16.8 months, while Group 2 has a delay in conversion to dementia with an average time of 19.44 months.

Data emerging from our study clearly show a key role of CRF in determining the clinical course of cognitive impairment in MCI patients. The presence of risk factors (dyslipidemia, hypertension, smoking, carotid atheromasy) seems associated with a higher probability of developing dementia (Verghese et al., 2009). Moreover, CRF appear to have an important influence on clinical evolution of the disease: patients with CRF show worse cognitive performances, frequently associated with behavioral disorders, depression and functional disability. It's worth to notice that the impairment of cognitive performances during observational time seems to be gradual with a linear trend in patients without CRF, while the group with risk factors shows a non-progressive cognitive worsening with peaks of lower scores in cognitive assessment, intervals of steadiness of clinical conditions, with the final achievement of a more severe cognitive impairment. The most important finding of our study is that the group with CRF has a more rapid conversion to AD compared with the control group (Ettorre et al., 2009, Staekenborg et al., 2009), with a median duration of disease-free interval about 3 months less than the group without risk factors. It would certainly be helpful to assess the impact of individual comorbidities on the time of conversion, but the lack of clinical data on post-follow-up time did not allow us to have enough information for a good statistical analysis. Somehow, the presence of CRF seems to cause a more rapid impairment of brain function through pathophysiological mechanisms that we do not perfectly know yet. We suppose that vascular pathology may lead to increased oxidative stress (Tabet et al., 2009) or activate a neuro-inflammatory response (Peters and Beckett, 2009), beginning the production of amyloid (Lopez et al., 2008). In fact, many studies show that cerebro-vascular pathology is closely associated with AD (Beeri et al., 2009); preventive strategies on risk factors could be useful for AD prevention. It is also important to notice that all patients who converted to dementia during observational time had MRI abnormalities consisting of cortical atrophy and ischemic subcortical pathology; on the contrary, only some patients with pathological changes in neuroimaging converted to dementia.

This study has several limits, but the results may encourage further research on the role of CRF in AD. The identification of risk factors that could be faced by pharmacological therapies and correct lifestyle, in fact, represents an important starting point for developing strategies to prevent dementia. This may lead to a significant reduction in the incidence of the disease in general population and to a better management of dementia-related disorders that usually cause severe disability of patients and overload of caregivers.

Conflict of interest statement

None.

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