Atrial fibrillation (AF) and cognitive impairment in the elderly: A case–control study

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ABSTRACT

AF is able not only to increase the risk of cognitive decline due to acute cerebrovascular events, but also to reduce cardiac output, with the consequence of impaired cerebral perfusion. The aim of this study was to evaluate the association between AF, dementia and depression in patients with negative anamnesis for past strokes. Our sample included 26 patients with a diagnosis of AF (paroxysmic, persistent, permanent) and 31 patients with sinus rhythm, enrolled as controls. All selected patients underwent a Multidimensional Geriatric Assessment in order to investigate cognitive and behavioral functions. Statistical analysis of results showed a greater frequency of latent cognitive impairment in patients with AF, even in the absence of memory disorders. As a matter of facts, AF patients showed Mini Mental State Examination (MMSE) scores significantly lower than those with sinus rhythm (p < 0.05) and Geriatric Depression Scale (GDS) scores higher than those without AF, evidencing a greater risk of depression too (p < 0.02). Results showed a statistically significant association between AF, depression and cognitive impairment in early stage. In conclusion, AF is not only associated with the risk of developing cognitive impairment, but it can also be considered as a risk factor for dementia and depression, even in the absence of medical history of past stroke.

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1. Introduction

Dementia is the most important neurological disorder in elderly (Lobo et al., 2000). Increased incidence of this disease is a direct consequence of aging (Bellomo et al., 2009). A major aim of scientific research is to identify specific risk factors for cognitive decline, in order to establish proper preventive strategies. The association of cardiovascular risk factors such as hypertension, atherosclerosis, type 2 diabetes, metabolic syndrome, obesity, dislipidemia and Vascular Dementia (VaD) has been fully explored in the past years. Moreover, a great amount of data recently published tends to identify a significant correlation between cardiovascular risk factors and Alzheimer’s Disease (AD), which is described by many authors as “a primarily vascular disorder” (Cecchetto et al., 2008; Duron and Hannon, 2008). There are many scientific evidences to support these hypotheses: (1) the large overlap between clinical features of VaD and AD; (2) drugs that are able to improve cerebral perfusion act effectively on the cognitive performance of patients diagnosed with AD; (3) the introduction, into clinical practice, of new techniques of cerebral perfusion (SPECT and CT-PET) for early diagnosis of preclinical forms of dementia, such as Mild Cognitive Impairment (MCI) (Polidori et al., 2001; Bellomo et al., 2009). Furthermore, many scientific studies identified a correlation between AF and AD in recent years. AF is the most common cardiac arrhythmia in the elderly and it is an important risk factor for thromboembolic events, as it increases 4–5 times the risk of ischemic stroke. In fact, it has been estimated that about 30% of strokes in patients between 80 and 89 years is the result of the consequences of this arrhythmia (Jozwiak et al., 2006; Bellomo et al., 2009). Nevertheless, AF is also involved in the formation of silent brain microinfarcts, which, together with the reduction in cardiac output, cause cerebral hypoperfusion, increasing the risk of neuronal degeneration and progressive cognitive decline. In the elderly, the reduction in cerebral blood flow (CBF) would be able to cause a true “neuronal energy crisis”, which would lead to a reduced adenosine triphosphate (ATP) synthesis and to an increase of cellular oxidative stress. This mechanism would be responsible for production and synthesis of abnormal proteins, functional alterations of brain neurotransmitters, accumulation of amyloid precursor protein (APP) and hyperphosphorylation of tau protein, which are typical histopathological lesions of AD (De la Torre, 2008). A histopathological study on the brain of AD patients showed the presence of microinfarcts and pathological changes of white matter located

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2. Patients and methods

Our research was led by Department of Aging of “Umberto I” Policlinico di Roma, “Sapienza” Università di Roma: 57 patients of both sexes, aged between 56 and 94 years were selected, 26 of them were diagnosed with AF (paroxystic, persistent, permanent) without a clinical history of acute cerebrovascular events (AF group). The remaining 31 individuals with sinus rhythm and no history of acute cerebrovascular events, were selected as control group (NAF group). All individuals enrolled in our study were further divided in different groups according to the presence of risk factors such as hypertension, hyperlipidemia, diabetes, tobacco smoke, in order to compare homogeneous groups of individuals in terms of comorbidity. Exclusion criteria of our study were: medical history of myocardial infarction, heart failure, unsteady carotid plaque diagnosed by ultrasound techniques. Patients with past diagnosis of vascular or neurodegenerative dementia were also excluded from the study. All individuals underwent MMSE and GDS, for cognitive and psycho-affective state assessment. After physical examination, all subjects underwent: 12 lead electrocardiogram, complete blood count, determination of serum electrolytes, Myoglobin, Troponin I, Total Creatinine Phosphokinase (CPK), CPK-MB, thyroid hormones, vitamin B12, folic acid, albumin, total cholesterol, HDL- and LDL-cholesterol levels, renal and liver functioning tests, in order to exclude secondary causes of cognitive decline and other comorbidities.

2.1. Features of AF group

AF group was composed of 26 patients, 11 males and 15 females with a mean age of 71.42 ± 8.30 (range 58–89) years and a mean education (years of study) of 15.8 ± 3.17 (range 0–13): 45% of the patients suffered from hypertension, 26% of them were treated with angiotensin receptor blockers (ARBs), 19% with angiotensin converting enzyme inhibitors (ACE-I). None of selected patients had clinical evidence of organ damage; 27.5% was found to be suffering simultaneously from hypertension, type-2 diabetes, dyslipidemia, and made use of antihypertensive, hypoglycemic and inhibitors of HMG-CoA reductase drugs; 14.7% had dyslipidemia controlled only by dietary measures. 12.2% of patients were diagnosed of reduced tolerance to carbohydrates (IGTT) by an oral glucose tolerance test (OGTT); 15% of patients turned out to be habitual tobacco smokers, 41% ex-smokers, 44% had never smoked. 48% of our sample made use aspirin, 9.5% of anticoagulants, 12.7% of Class III Anti arrhythmics drugs. Symptoms of AF in our sample were: 36.1% pulse-pounding, 29.4% dyspnea, 14.3% fatigue, 10.1% palpitations. 8.1% of patients had no symptoms. All patients in AF group were diagnosed with AF (30.8% paroxystic, 26.9% persistent, 42.3% permanent).

2.2. Features of NAF group

Thirty-one subjects with sinus-rhythm were included in the control group: 14 males and 17 females with a mean age of 72.10 ± 8.53 (range 56–94) years and mean education (years of study) of 7.0 ± 3.78 (range 0–18). In the control group 38% of individuals suffered from hypertension, 19.5% from all the diseases mentioned above. 19.3% of patients turned out to be habitual tobacco smokers, 43% ex-smokers, 37.7% had never smoked. 51% of the sample made use of aspirin, 6.4% of anticoagulants, 19.6% of HMG-CoA reductase, 23% of hypoglycemic drugs; 11% of antihypertensive drugs.

2.3. Statistical analysis

Data were analyzed using SPSS for Windows (13th version). All continuous variables were expressed as mean ± S.D. Statistical analysis was performed using Student’s t-test for independent samples, after having divided the patients according to the presence of AF into the AF and NAF groups. A p < 0.05 was regarded as minimum level of statistical significance. All results were then expressed graphically, for a better view of data obtained.

3. Results

The aim of our study was to investigate the association between AF and cognitive decline in elderly patients with cardiovascular risk factors. The analysis involved 57 patients: 25 males and 31 females, with an average age of 71.76 ± 8.4 years, average education of 7.58 ± 3.48 years of school and 47.5% of comorbidities for cardiovascular risk factors. Patients with a medical history of dementia and cerebrovascular accidents (stroke or TIA) or showing signs of hemodynamic instability were excluded from our study. All diseases were under optimal medical treatment. The ability of subjects included in our study to undertake a complete test battery was full, and none of them was excluded from the research protocol. In all cases the complete test battery was administered in 25 min.

After adjustments for age, education, multiple cardiovascular risk factors, AF patients obtained lower MMSE scores than patients with sinus rhythm, showing an increased prevalence of cognitive impairment, even without cognitive or memory disorders. Average MMSE score, adjusted for age and education, was 26.85 ± 1.85 for AF group vs. 27.56 ± 1.47 for NAF group (p < 0.05) (Fig. 1); 31% of patients in AF group showed a MMSE score between 26 and 24, which indicates the presence of a borderline cognitive framework, compared to 26% of NAF patients (Fig. 2). The trend of the scores was related with age and education, as reflected in the summary graphs.
In particular, cases scored lower than controls in the items of recording and registration memory, but also in the items of attention and calculation. Patients in AF group had also greater difficulty in correctly finishing the interlocking pentagons test. This result, however, was detected only in subjects with lower MMSE scores (<26). There was no correlation between duration of AF and patients’ age. Furthermore, there was no correlation between duration of AF and performance in any of the neuropsychological tests. When the data were examined to determine the effect of duration of AF on outcome in the two different sex groups there was no significant relation for male or female subjects. Moreover, there was no statistically significant association between neuropsychological test scores and use of different drugs for the prevention of cerebrovascular events.

AF group has also shown an increased risk of depression, 15% of AF group vs. 6% of NAF group (p < 0.02) (Fig. 3). Patients of AF group more frequently reported loss of interests, unhappiness, sadness, presence of memory problems, perception of health problems, fear of adverse events. There was no correlation between duration of AF and GDS scores.

4. Discussion

The vascular hypothesis of AD, first proposed in 1993, provides substantial evidence that suggests that vascular risk factors play a critical role in the development of cognitive decline and AD during aging (De la Torre, 2008). This research was primarily a pilot study to explore our hypothesis that patients with and no history of stroke are at increased risk of cognitive impairment and depression as a result of silent cerebral infarction and reduction in CBF caused by decreased cardiac output. The presence of AF was associated with poorer performance on the test battery, although significant differences between cases and controls existed particularly in tests for recording and registration memory, and in tests for attention and calculation. This suggests that AF has particular effects on memory and new learning, which is consistent with evidence that dementia is linked to new learning and memory deficits, and that multi-infarct dementia in particular is linked to explicit as opposed to implicit memory. It is not possible to determine from our data whether patients had coexistent dementia and cerebrovascular disease to account for their cognitive performances. However, we believe that sporadic AD is a vascular disorder with neurodegenerative consequences and needs to be treated and managed as such. Epidemiologic studies on vascular risk factors, together with preclinical detection tools for AD (cerebral perfusion imaging studies) are proof that cerebral hypoperfusion is one of the earliest pathological signs in the development of cognitive failure. Vascular risk factors involving heart disease and stroke in the elderly who already possess a dwindling cerebrovascular reserve due to advanced age contribute to further decline in CBF resulting in unrelenting brain hypoperfusion. Brain hypoperfusion, in turn, can reach a critically attained threshold giving rise to a neuronal energy crisis via reduced ATP synthesis. The ensuing metabolic energy crisis initially carves up ischemic-sensitive neurons in the hippocampus and posterior parietal cortex setting up cognitive meltdown and progressive neurodegenerative and atrophic changes in the brain. Neuronal energy compromise accelerates oxidative stress, excess production of reactive oxygen species, aberrant protein synthesis, ionic membrane pump dysfunction, signal transduction impairment, neurotransmitter failure, abnormal processing of APP resulting in beta-amloid deposition and axonal microtubule disruption from tau hyperphosphorylation. The energy metabolic changes leading to oxidative stress and cellular hypometabolism precede clinical expression of AD (De la Torre, 2008).

The number of patients of our study is maybe too small, consequently subgroup analysis may be inappropriate. Nevertheless, we have shown a trend toward poorer performances on detailed neuropsychological testing in patients with AF and no history of stroke when compared with matched controls in sinus rhythm. The present study was a community based project and therefore imaging was not performed. In any future larger study, MRI would be essential to determine whether cognitive impairment in subjects without AF correlates with silent cerebral infarction and low CBF. We think that our hypothesis should be further examined in a prospective interventional study to determine whether antithrombotic therapy may protect against cognitive decline.

Cognitive decline and dementia have a high incidence and a strong social impact. Despite extraordinary progresses, many things about etiology and development of an effective therapy remain unclear. The importance of preventive or therapeutical treatment strategies accounts for the growing interest in research of risk factors and pathological conditions associated with the development of dementia. Many risk factors for dementia are indeed very common conditions (hypertension, type 2 diabetes, dyslipidemia, tobacco smoking, etc.). Unfortunately, associations between these pathological conditions and dementia need further investigations.

5. Conclusion

Our results are confirmed by other studies. However, the pathophysiological mechanisms linking AF and AD are still almost completely unknown. The full comprehension of the neuropathological pathways leading to AD opens new opportunities to prevent and treat this disease. These new findings can give new hope to thousands of patients that already suffer from devastating effects of AD and to all those who have a higher probability to get demented, even if they still do not show the clinical symptoms of this dramatic pathology.

Conflict of interest statement

None.

References

