Research Article

Cardiovascular Risk Factors and Cognitive Impairment: A Prospective Study

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Abstract

Dementia was affecting 47 million people worldwide in 2016, representing a huge economic and social burden. Considering the increase in the life expectancy, the incidence of dementia is increasing. The need of early diagnosis and therapeutic approach has been driving research over the last decades, shading light over various aspects of cognitive impairment. Great interest has been given to the potential intersection of different pathological entities in the neurodegenerative process, making the disease a result of the complex network of modifiable and not modifiable risk factors. Interest has been driven to the major cardiovascular risk factors, such as systemic hypertension, dyslipidaemia and diabetes mellitus, with attention in mid-life. In the current prospective, observational study we evaluated a cohort of 127 non-selected subjects attending the Outpatient Neurology Clinic of the Hospital of Livorno, Tuscany. No correlation was obtained between each major cardiovascular risk factor and cognitive function, as assessed by MMSE (Mini-Mental State Examination) in the whole cohort. While dividing patients according to age (older or younger than 75 years), we observed a positive relationship (although only approaching the statistical significance) between the burden of cardiovascular risk factors and cognitive impairment, in the oldest group of patients only. Our results, even if preliminary and coming from a relatively small group of patients, are in line with the literature, and support the importance of actively acting on cardiovascular risk factors, especially early in life, to counteract the risk of cognitive impairment and dementia with increasing ageing.

Introduction

According to the World Alzheimer's report, the prevalence of dementia in 2016 was 47 million people worldwide, number expected to exceed 130 million by 2050 [1]. Alzheimer's Disease (AD) is the most common type of dementia, accounting for 50-70% of all cases. Amyloid and Tau deposition is known to be the neuropathological hallmark of the disease, but during the last decades of life other factors have been recognised to play a role in the physiopathology of neurodegeneration, making Alzheimer's disease a multifactorial entity. Vascular alterations play a role the disease development, and vascular changes are a common characteristic in Alzheimer's subjects. Both atherosclerosis and small vessel disease lead to the reduction of cerebral blood flow and consequent tissue suffering [2] , and different studies demonstrated that either micro or macro vascular diseases are associated with cognitive impairment independently of AD physiopathology [3]. The connection between Cardio Vascular (CV) risk factors and cognitive impairment, AD in particular, is worldwide recognised and extensively studied. Few genetic mutations and polymorphisms are shared between AD, CV and cerebrovascular diseases, such as APO e4 [4] and various polymorphisms of the Methylene Tetra Hydro Folate Reductase (MTHFR), dealing with high homocysteine levels [5]. The major risk factors associated with CV and cerebrovascular diseases such as age, gender, Diabetes Mellitus (DM), systemic hypertension and dyslipidaemia have been widely studied in relation to cognitive impairment and dementia. A higher score in the Framingham Cardiovascular Risk Profile (FCRP) is linked to worse cognitive performance, more prominent brain at-

rophy and white matter changes and, is considered a predictor of conversion from Mild Cognitive Impairment (MCI) to AD [6-9]. A specific risk score, the Cardiovascular Risk Factors Aging and Dementia (CAIDE) have been recently developed, which takes into account systemic blood pressure, circulating cholesterol and DM to predict the risk of dementia over 20 years among middle aged people [10]. Chronic hypertension, determining morphological and functional changes in the vessel walls has been linked to brain tissue hypo-perfusion and consequent neuronal damage, with different impact depending on the age of onset and the duration of the disease [5]. The correlation between high cholesterol and AD/MCI is complex, since peripheral cholesterol levels do not mirror the levels in central nervous system. However, taking into account that hypercholesterolemia leads to atherosclerosis, and several epidemiological studies showed a relationship between cholesterol levels and AD, different trials evaluated the use of statins in reducing the incidence of AD [5]. Type 2 DM (T2DM) is another factor interestingly linked to AD. Different epidemiological studies showed that T2DM or impaired fasting glucose increase the risk of dementia, and many studies with anti-diabetic drugs have been carried out, with inhomogeneous results [11,12].

The current study aimed to assess the actual presence of the major CV risk factors in patients with mild to moderate cognitive impairment, consecutively seen in the outpatient clinic of a first level hospital in Tuscany. The association between the burden of CV risk factors and cognition was also assessed.

Keywords: Ageing; Cognition; Cardiovascular Risk; Dementia; Diabetes Mellitus; Hypertension

Patients and Methods

We enrolled 127 patients [76 women, mean age (± SD) 78.2 ± 7.1 years] consecutively attending the outpatient Neurology Clinic of the Hospital of Livorno, Tuscany. All the patients gave their written informed consent. The study was designed according to the declaration of Helsinki. The following demographic and clinical information were recorded at the first visit: age, gender, current medication, past medical history. In addition, a first cognitive assessment was done by the Mini Mental State Examination (MMSE). As part of the visit, a routine test battery was completed, including full blood count, liver, thyroid and renal function tests, lipid profile and fasting glucose levels. According to the medical history and the result of the fasting serum glucose level, patients were classified as: Impaired Fasting Glucose (IFG, fasting glucose level >110 and <125 mg/dl), diabetic (fasting glucose level >126 mg/dl) and euglycemic (fasting glucose level <110 ml/dl). A group of patients with dyslipidaemia was selected according to the medical history, concomitant medications and high LDL c value (100 mg/dl was used as the cut-off level). Systemic Blood Pressure (BP) was measured with the patient lying and resting for few minutes before the measurement; population was divided into two groups,

according to the presence or absence of hypertension (diastolic BP >90 and systolic BP >140 mmHg), considering the medical history, the current medications and the blood pressure values.

The population was analysed regarding the prevalence of the major cardiovascular risk factors, such as hypertension, DM/IFG and dyslipidaemia, as well as the cognitive performance as measured at the first clinical evaluation. We also divided the population into two groups according to age (older or younger than 75 years) and the prevalence of the CV risk factors in each group was assessed by using the Chi-square test. Finally, the possible relationship between the mean burden of CV risk factors and quartiles of MMSE score was evaluated.

Results

One-hundred-twenty-seven consecutive patients with cognitive impairment, at their first referral to the Neurology Outpatient Clinic in Livorno were enrolled. Within the entire population, the mean MMSE score was 20.6/30 (SD 5.1), the mean glucose level was 111.61 (SD 62.36), mean total cholesterol was 207.36 (SD 42.28) and the mean LDL cholesterol was 129.92 (SD42.28). 52.8 % of the overall population had a diagnosis of dyslipidaemia, 53% of the population had a diagnosis of hypertension and 33.7% had impaired fasting glucose/diabetes mellitus. Considering as cardiovascular risk factors the diagnosis of dyslipidaemia, hypertension and IFG/DM, within the cohort evaluated, 43.3 % had 1 risk factor, 31.9 % had 2 risk factors and 7.9 % had 3 risk factors; 10% of the population had no risk factors. [Table 1] summarise the characteristics of the population presented

	Whole cohort (n=127)	Women (n=76)	Men (n=51)
Age	78.2 ± 7.1	78.5 ± 7.1	77.6 ± 7.2
MMSE	20.6 ± 5.1	20.2 ± 4.9	21.0 ± 5.4
Hypertension	53.10%	54.20%	51.40%
IFG/DM	33.70%	59.80%	40.20%
Dyslipidemia	52.80%	59.80%	40.20%

Table 1: Demographic characteristics of the population.

Women were older [78.5 (± 7.1) Vs 77.6 (± 7.2), respectively] with lower MMSE score (20.2 ± 4.9 Vs 21.0 ± 5.4, respectively) than men. Moreover, the burden of major CV risk factors was higher in the female group than in men: hypertension 54.2% Vs 51.4%; IFG/DM 59.8% Vs 40.2%; dyslipidaemia 59.8% Vs 40.2%, respectively.

In the whole cohort, 72% of the subjects were older than 75 years (mean 82.5 ± 3.8; 58% women and 42% men). In this patients' group the clinical characteristics were as follows: MMSE score 20.30 ± 5, fasting glycaemia 121.1 ± 75.4 mg/dl, total cholesterol 207.1 ± 41.2 mg/dl, LDL c 125.8 ± 35.0 mg/dl. IFG was

observed in 38% of the subjects and 39.5% were affected by T2DM, 53.1% had systemic hypertension and 60.9% dyslipidaemia (p=0.01 Vs younger patients) [Table 2]. Thus, 50% of them showed one, 27.6% two and 10.5% 3 major CV risk factors while, only 11.8% had no CV risk factors.

	Older than 75 years (n=91, 58.0% F)	Younger than 75 years (n=36, 60.6% F)
Age	82.5 ± 3.8	69.4 ± 4.8
MMSE	20.3 ± 5.0	21.8 ± 5.4
Hypertension	53.10%	50.00%
IFG	38.00%	23.10%
DM	39.50%	30.30%
Dyslipidemia	60.9%*	48.10%
*p=0.01, Chi square test		

Table 2: Cardiovascular risk factors among younger and older population.

The quartiles of MMSE score in the older group of patients were as follows: Q1: 8-17; Q2: 18-21; Q3: 22-24.5; Q4: 24.6-29. Although only approaching the statistical significance, the burden of major CV risk factors resulted higher among patients with the lowest percentile of MMSE (p=0.09, Figure-1). No association was otherwise observed between CV risk factors and percentiles of MMSE score in the younger group of patients.
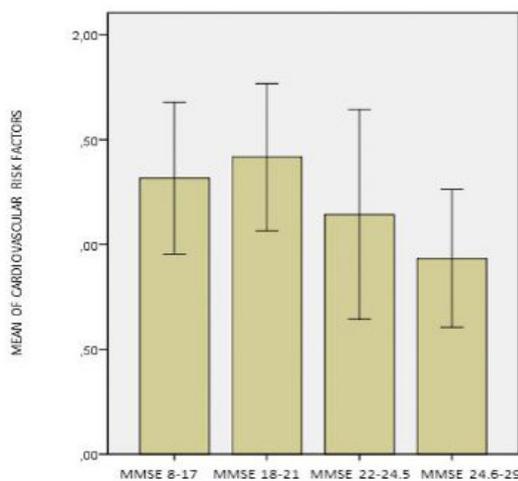
Figure 1: Mean distribution of cardiovascular risk factors (hypertension, dyslipidaemia and IGF/DM) according to different quartiles of MMSE (defined as shown), in the study population older than 75 years of age.

Discussion

Alzheimer's disease is a complex and heterogeneous syndrome, with an incidence increasing together with the increased life expectancy, affecting one in three subjects over 85 years of age, and representing a huge social and economic burden. Over the last decades, research made huge steps in understanding the complex physiopathology of AD.

In our prospective study, we evaluated a population referred to the Neurology Outpatient Clinic in Livorno, Tuscany. The subjects presented with cognitive impairment, and all of them underwent detailed medical assessment and routine blood test examination. After dividing the population in two different groups according to age, with a cut off of 75 years, we noticed that among older patients those with a better cognitive profile (i.e. the highest quartile of MMSE) showed also a lesser burden of major CV risk factors, showing better glycaemic control and lower prevalence of dyslipidaemia and systemic hypertension. The relationship only approached the statistical significance, probably be due to the small size and the heterogeneity of the sample. Moreover, the results come from a first evaluation in the outpatient clinic, where cognitive impairment was assessed but no definite diagnosis was made. Our results, even if preliminary, are in line with what is known from the literature. Different epidemiological studies supported the role of hypertension in cognitive impairment [5,13], but the causal relation is still debated; different studies evaluated the efficacy of anti-hypertensive treatment in reducing the incidence of AD or lowering the progression, with encouraging results [14,15]. A recent meta-analysis evaluated the impact of midlife CV risk factors on the incidence of AD; while the systolic blood pressure wasn't associated with AD, high diastolic blood pressure was strongly associated [16]. The same meta-analysis found strong association between AD and hypercholesterolemia, obesity, and DM [16]. According to our results, particularly important is the presence of CV risk factors early in life. A recent work from Rovio et al evaluated the cognitive performance, visual and episodic memory and visuospatial associative learning, in a population based cohort followed up for 31 years, starting during childhood. Interestingly, high blood pressure and hypercholesterolemia in young age, together with the smoking, resulted in poorer cognitive performance in the following decades of life [17]. Hypercholesterolemia itself, especially in midlife, has been recognised as an independent risk factor for AD in several epidemiological studies, and a potentially protective role of statins has been evaluated, with promising results [18]. The hyperglycaemic state is considered to have a role in neuronal damage in dementia, with a direct toxic effect, through the advanced glycosylated end products and oxidative stress, and indirectly due to the osmotic stress impairing the blood brain barrier integrity [19]. The link between diabetes and AD is also widely studied and accepted, and many preclinical and clinical trials are ongoing to evaluate the potential efficacy of antidiabetic drugs on AD [20].

A limitation of the study is the small sample size and that the data collected were from the first evaluation at the Outpatient Clinic, and not selected basing on the cognitive concern or specific phenotype. In conclusion, our study is in line with the literature,

showing that the presence of one or more major CV risk factor is correlated with worse cognitive performance, which become more evident with increasing age. These data support the importance of actively acting on CV risk factors, especially early in life, to counteract the risk of cognitive impairment and dementia with increasing ageing. Further large interventional studies with better defined cognitive concern and specific phenotype evaluation are needed to outline the best therapeutic approach.

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