ARTICLE

Late Life Vascular Risk Factors and Their Association with Dementia and Alzheimer's Disease

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ABSTRACT

Background: Epidemiological studies have demonstrated associations between higher levels of vascular risk factors in midlife and later development of dementia, particularly Alzheimer's disease (AD). However, in elderly subjects with dementia, some studies have shown that these associations may decrease or even reverse. Therefore, the study aimed to find the association between late life cardiovascular risk factors and neurodegenerative dementia in general and AD in particular.

Methods: It is a retrospective case control study using electronic medical records that included elderly patients that were reviewed in Ahmadi hospital geriatric clinic, Kuwait, from the period of 1/7/2019 to 1/2/2020. Two hundred and three (203) elderly patients with neurodegenerative dementia (study group) were recruited for this retrospective study and compared to two hundred and one (201) controls with normal cognition for the presence of vascular risk factors.

Results: The study included 404 subjects. Age ranged from 60 to 107 years (mean age 78.79, ± 8.13 SD). AD was found to be the most prevalent type of dementia in the study group, as 49.3% (100/203) of the demented patients were diagnosed with AD.

No significant statistical association was found between vascular risk factors and dementia (P>0.05), except for obesity which showed a negative association (P<0.001). Regarding AD, no statistical significance was found between AD and diabetes, hyperlipidemia, smoking nor atrial fibrillation. On the other hand, the authors found obesity and hypertension more prevalent in the normal cognition group (negative association with P value <0.001, 0.05 respectively).

Conclusions: The results of the study support an emerging concept that, while elevated levels of vascular risk factors in midlife increase the risk of development of dementia and AD later in life, once dementia begins, these associations may be diminished or reversed in the elderly.

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1. Introduction

Dementia prevalence rates are increasing at alarming proportion in many regions of the world and are related to population aging [1]. The Global Burden of Disease 2010 revealed that neurologic conditions, including dementia, are the third leading cause of years lived with disability globally [2]. Dementia is a condition characterized by a progressive decline in several cognitive functions (including learning and memory, complex attention, language, perceptual-motor ,executive function , or social cognition from previous levels of functioning), that interfere significantly with the ability to maintain daily living activities in both social and professional aspects [1,3].

Although dementia is a syndromic entity, there are various subtypes of dementia that vary in their etiology, form of presentation, clinical course and associated disorders. Alzheimer's disease (AD), vascular dementia and mixed forms of AD with cerebrovascular involvement component accounts for the most prevalent subtypes. Other forms of neurodegenerative dementias (e.g. Parkinson's disease associated dementia, frontotemporal dementia/Pick's disease, Lewy body dementia, Huntington's disease,) are much less frequent [4].

Age is the most well established risk factor for dementia [5]. In addition, genetic factors (apolipoprotein E) and vascular risk factors may play an important role as well [6].

The relationship between cardiovascular disease and dementia is of particular interest as both have increased prevalence with age, moreover, recent studies have shown that changes in sirtuin expression with aging could have a critical role in the development of metabolic syndrome, cardiovascular diseases and neurodegeneration.

Numerous epidemiologic studies have observed associations between vascular risk factors (like diabetes mellitus, hypertension, and hyperlipidemia) and the risk of dementia, especially for AD [8-12]. However, despite that dementia has been reported to be associated with higher levels of vascular risk factors measured in midlife in prospective epidemiological studies, some studies have shown that these associations in elderly subjects with dementia may decrease or even reverse [13-19].

Therefore, our study aimed to find the association between late life cardiovascular risk factors and neurodegenerative dementia in general and AD in particular.

2. Materials and Methods

A retrospective case control study using electronic medical records (EMR) that included elderly patients (60 years and older) that were reviewed in the geriatric clinic of Ahmadi hospital, Kuwait, from the period of 1/7/2019 to 1/2/2020.

Two hundred and three (203) elderly patients with dementia (study group) were recruited from the EMR and compared to two hundred and one (201) controls with normal cognition to find the association of dementia with vascular risk factors.

Inclusion criteria:

• The study group: patients were included in the study if they had a diagnosis of neurodegenerative dementia (such as Alzheimer's disease, vascular dementia, mixed forms of AD, frontotemporal dementia, Parkinson's disease associated dementia, dementia with Lewy bodies, progressive supranuclear palsy and corticobasal degeneration dementia). Patients who had a diagnosis of dementia were identified based on clinical history, neurological examination, cognitive testing and neuro-imaging. All patients had undergone brain computerized tomography, magnetic resonance imaging or both and routine laboratory tests including serum vitamin B12 and thyroid function.

• The control group: for each case in the study group, an individual with normal cognition is selected randomly from the same EMR, matched to the case based on gender and age (±2 years).

Exclusion criteria: patients with history of brain injury, cognitive dysfunction due to medical illnesses or medications, mild cognitive impairment, hydrocephalus, brain cancer and other major psychiatric diseases.

The collected data included the following:

• Age, sex and education;

• History of vascular risk factors including hypertension diabetes mellitus, hyperlipidemia, obesity (body mass index{BMI}≥30), smoking and atrial fibrillation;

• History of ischemic heart disease.

Our sample size was calculated using STATA program, setting the type-1 error (α) at 0.5 and the power (1-β) at 0.8. An effective sample includes ≥400 patients in two groups (cases and controls) was needed to produce a statistically acceptable figure.

Statistical Analysis

SPSS statistics (V. 25.0, IBM Corp., USA 2017-2018) software was used for the statistical analysis of data. Descriptive statistics for the continuous variables were reported as means and standard deviations, and categorical variables were summarized as frequencies and percentages. Categorical variables were compared using the Chi-square test(χ^2 test). The level of statistical significance was set at $p < 0.05$.

3. Results

The study included 404 subjects :203 dementia patients and 201 subjects with normal cognition.

Age of the study subjects ranged from 60 to 107 years (mean age 78.79, ± 8.13 SD) and the general characteristics of the studied population are shown in Table 1.

Table 1. General characteristics of the studied population (N = 404)

		No. = 404
Age	Mean ± SD Range **Age groups:** 60-69 years: 47 patients (11.6%) 70-79 years: 167 patients (41.3%) 80-89 years: 160 patients (39.6%) 90 or more: 30 patients (7.4%)	78.79 ± 8.13 60 - 107
Education	Illiterate literate	82 (20.3%) 322 (79.7%)
Sex	Female Male	263 (65.1%) 141 (34.9%)
Dementia	Normal cognition Cases of dementia	201 203
Hypertension	Negative Positive	64 (15.8%) 340 (84.2%)
Diabetes mellitus	Negative Positive	138 (34.2%) 266 (65.8%)
Hyperlipidemia	Negative Positive	77 (19.1%) 327 (80.9%)
Obesity	Negative Positive	221 (54.7%) 183 (45.3%)
Smoking	Negative Positive	377 (93.3%) 27 (6.7%)
Atrial fibrillation	Negative Positive	350 (86.6%) 54(13.4%)
Ischemic heart disease	Negative Positive	306 (75.7%) 98 (24.3%)

Among the dementia group, AD was found to be the most prevalent type of dementia, as 49.3% (100/203) of the demented patients were diagnosed with AD. Vascular dementia was the second most prevalent dementia type followed by mixed dementia (25.6% and 7.8% respectively). Other dementia subtypes frequencies are shown in Table 2.

We observed no significant statistical association between vascular risk factors and dementia (P>0.05), except for obesity which showed a negative association (P<0.001). (See Table 3)

Table 2. Prevalence of dementia subtypes among the dementia (study) group

		N	%
Type of dementia	Alzheimer's disease dementia	100	49.3%
	Vascular dementia	52	25.6%
	Lewy body dementia	11	5.4%
	Mixed dementia	16	7.8%
	Parkinson's disease dementia	14	6.9%
	Corticobasal degeneration dementia	3	1.5%
	Prion disease dementia	1	0.5%
	Fronto temporal dementia	4	2%
	Progressive supranuclear palsy	2	1.0%

Table 3. Association of vascular risk factors in dementia compared to normal cognition group

		Dementia (N=203)		Normal cognition (N=201)		X^{2*}	P value
		N	%	N	%		
Hypertension	yes	164	80.8%	176	87.6%	3.48	0.06
	no	39	19.2%	25	12.4%		
Diabetes mellitus	yes	131	64.5%	135	67.2%	0.31	0.58
	no	72	35.5%	66	32.8%		
Dyslipidemia	yes	160	78.8%	167	83.1%	1.19	0.28
	no	43	21.2%	34	16.9%		
Smoking	yes	10	4.9%	17	8.5%	2.02	0.16
	no	193	95.1%	184	91.5%		
Obesity	yes	69	34.0%	114	56.7%	21.05	<0.001
	no	134	66.0%	87	43.3%		
Atrial fibrillation	yes	26	12.8%	28	13.9%	0.11	0.74
	no	177	87.2%	173	86.1%		

*Chi Square test

Regarding AD, no statistical significance was found between AD and diabetes, hyperlipidemia, smoking nor atrial fibrillation. On the other hand, we found obesity and hypertension more prevalent in the normal cognition group (negative association with P value <0.001, 0.05 respectively). (See Table 4)

Table 4. Relation between Alzheimer disease and vascular risk factors

		Alzheimer's disease (N=100)		Normal cognition (N=201)		X^{2*}	P value
		N	%	N	%		
Hypertension	yes	79	79.0%	176	87.6%	3.78	0.05
	no	21	21.0%	25	12.4%		
Diabetes mellitus	yes	63	63.0%	135	67.2%	0.51	0.47
	no	37	37.0%	66	32.8%		
Hyperlipidemia	yes	81	81.0%	167	83.1%	0.20	0.66
	no	19	19.0%	34	16.9%		
Smoking	yes	3	3.0%	17	8.5%	3.21	0.07
	no	97	97.0%	184	91.5%		
Obesity	yes	28	28.0%	114	56.7%	22.10	<0.001
	no	72	72.0%	87	43.3%		
Atrial fibrillation	yes	15	15.0%	28	13.9%	0.06	0.80
	no	85	85.0%	173	86.1%		

*Chi Square test

4. Discussion

During the past decade, growing evidence supporting a statistical linkage between vascular factors and neurodegenerative dementia have originated from studies of AD, or from studies in which AD was most probably the commonest cause of dementia [20]. Previously, the "vascular hypothesis" of Alzheimer's disease was proposed by numerous early investigators including Alzheimer himself, as they suggested that the disease was triggered by cerebral atherosclerosis. However, during the period from 1950's and 1960's, several postmortem studies failed to find an association [21]. In 1993, apoE-ε4 allele was discovered to be associated with Alzheimer's disease [22], which brought back interest in the vascular hypothesis as the ε4 allele by this time had been demonstrated to be associated with coronary atherosclerosis. Thereafter, a series of clinical and epidemiologic studies revealed that vascular risk factors are risk factors for Alzheimer's disease [23-25].

In the present study, no significant statistical association between hypertension and dementia was found and surprisingly we observed a significant negative association between hypertension and AD, with more cases of hypertension in the non demented group.

Studies investigating the association between cognitive function and blood pressure have shown conflicting results, as studies in literature have reported both positive [26,27] and negative [28,29] associations between hypertension and cognitive dysfunction. Furthermore, the relationship between cognitive functions and blood pressure is more complicated and not just linearly correlated. Chronic hypertension may predispose to cognitive impairment and dementia [30,31], however, a decline in blood pressure can be demonstrated in the time period before the onset of dementia and afterwards [32,33]. One explanation of this association is that: the neurons that are involved in vasomotor regulation in the brain stem are lost in Alzheimer's disease which could result in reduced blood pressure [34].

Despite that type 2 diabetes mellitus is a well known risk factor for stroke [35], studies investigating its association with dementia have reported contradicting results. Previous studies have reported that diabetes comes with a 25% to 91% increased risk of developing dementia [36,37]. One recent research has shown that poor health, including obesity and diabetes, in early adulthood ups dementia risk [38]. On the other hand, other longitudinal studies did not observe such associations [39,40]. In our study, no statistically significant association was found between diabetes mellitus and dementia or Alzheimer's disease. Similar results have been reported by the Honolulu Asian Study, in which the investigators did not find a positive association between diabetes mellitus and Alzheimer's disease [41].

In the present study, we did not find a significant association between hyperlipidemia and dementia or AD, which is consistent with the results reported by other studies [42,43]. In the literature, evidence for the association between cholesterol levels and the risk of dementia has been inconsistent. Some studies have shown no association or an inverse association with total cholesterol levels measured in later life, whereas those studies that reported a positive association examined the effect of mid-life total cholesterol levels with longer follow-up. The association between total cholesterol and risk of dementia seams to vary with age at measurement (mid-life [<65 years] or later life [≥65 years]) and follow-up duration [44-49].

Prospective studies on non demented individuals demonstrated that smokers often have higher risk for developing dementia, including Alzheimer's disease [50,51]. In our study, we did not find a significant association between smoking and dementia or Alzheimer's disease (we had a small number of smokers in our study subjects as only 6.7% of the total study subjects were smokers).

Surprisingly, we observed negative association between obesity and dementia. Obesity is a well known risk factor for cancer, type 2 diabetes and cardiovascular disease, and it has been suggested as an independent risk factor for dementia and Alzheimer's disease as well [52-54]. Fitzpatrick AL et al. have observed higher risk of dementia among obese individuals (BMI≥30), as compared to those with normal body mass index (BMI 20~25) at 50 years of age. Whereas, a reverse association was observed between BMI and risk of dementia at ≥65 years of age [55]. Studies investigating the relation between obesity and incident dementia used to measure body mass index (BMI) or adiposity in mid rather than late life. The majority of these studies have linked mid-life obesity to increased risk of dementia later in life [56,57]. In contrast, low BMI in later life is related to the development of dementia, since weight loss is an early sign of the disease rather than a real risk factor [58].

Lately, weight loss has been linked to preclinical and prodromal AD stages up to 20 years before beginning of the symptoms [59-61]. This prolonged duration of weight loss in preclinical AD might mask the association between obesity in late life and AD, and might elucidate the "obesity paradox".

Other hypotheses to explain for the association of weight loss and AD: non-specific effects of neurodegenerative diseases, such as nihilistic apathy that may

exist in the terminal stage of dementia, decreased activities of daily living (i.e., grocery shopping, cooking), that may predispose to under nutrition [62-64] which could also lead to activation of Sirtuin 1 and reversal of obesity and metabolic syndrome [65].

Some limitations needed to be mentioned in the present study. First, the retrospective design. Second, no autopsy was available to confirm diagnosis. Despite these limitations, to the best of our knowledge, this study is the first study investigating prevalence of dementia subtypes and association with vascular risk factors in our region.

5. Conclusions

The results of our study support an emerging concept that, while elevated levels of vascular risk factors in midlife increase the risk of development of dementia and AD later in life, once dementia begins, these associations are found to be diminished or reversed in the elderly (66,67), probably due to continuous weight loss with advancing dementia and disease affection of vasomotor centers in the brainstem. Future longitudinal studies starting from midlife to death, investigating the association of clinical and neuropathological aspects of dementia with cardiovascular risk factors and the role of sirtuin 1 activation are needed.

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Conflicts of Interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Consent to Participate

The requirement for participant informed consent was waived because it was a retrospective study.

Ethical Approval

This research study was conducted retrospectively from data obtained for clinical purposes. The study was approved by the local institutional review board.

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