

Case Report: Medical Risk Factors for Dementia; A Case-Control Study



Hossein Ghasemzadeh^{1*}, Ahmadali Akbari Kamrai¹, Yadollah Abolfathi Momtaz¹, Mehdi Rassafian¹, Fatemeh Nourhashemi¹, Robab Sahaf²

1. Department of Ageing, Research Center on Ageing, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran.

2. Department of Occupational Therapy, Faculty of Allied Health Sciences, Kuwait University, Kuwait.



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ABSTRACT

Objectives: Dementia is the fifth cause of death in older adults with the most significant financial, social, and caring burden on health systems across the world. The aim of this study was to determine the most common medical risk factors for dementia in the retired population.

Methods: A case-control methodology was used for this study, within which 180 patients with dementia were compared to 371 controls for medical risk factors in the National Iranian Oil Company (NIOC) in 2017. Participants in the case and control groups were matched in terms of age, educational level, and sex. The logistic regression was employed to estimate Odds Ratios (OR), using SPSS software.

Results: The majority of the participants were male (55%) and married (69%) with a mean age of 73.14 (SD=9.11) and high school education (38%). The results of the adjusted logistic regression showed a significant association among dementia and chronic and acute vitamin D3 deficiency (more and less than 1 year) (OR=4.73, P<0.001, OR=7.50, P<0.001, respectively), cancer history (OR=15.31, P<0.001), and chronic anemia (OR=5.95, P<0.001).

Discussion: The results of this study suggest vitamin D3 deficiency, cancer, and anemia history as probable risk factors for dementia. Thus, managing or controlling these risk factors may effectively delay or prevent the onset of dementia for the individuals.

* Corresponding Author:

Hossein Ghasemzadeh, Md.

Address: Department of Ageing, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran.

Tel: +98 (919) 2196964

E-mail: hghassem361@gmail.com

Highlights

- Severe vitamin D3 deficiency, cancer, and anemia history can increase the risk of dementia.
- The risk of dementia in individuals with chronic vitamin D deficiency was lower than the ones with acute vitamin D deficiency.

Plain Language Summary

The fifth cause of death in older adults, dementia, is a neurodegenerative disease, causing memory loss and functional impairment. The massive financial burden of care for patients with dementia and the lack of an effective treatment for postponing or stopping dementia make it an indispensable task to identify and manage preventable medical risk factors. In a case-control study, we compared 180 patients with dementia with 371 non-demented controls for medical risk factors. Among the surveyed medical risk factors, only acute and chronic vitamin D3 deficiency, anemia, and cancer history increased the risk of dementia for the individuals. Thus, managing or preventing these risk factors can be an effective preventive measure against dementia.

1. Introduction

Today, nearly 50 million people with dementia are living in the world, and it is believed that the figure will have tripled in 30 years [1]. Dementia syndrome is primarily seen in later life and results in memory accompanied by the impairment of other aspects of function [2]. A noticeable rise in life expectancy and global population aging have been deemed to be the leading causes for this phenomenon. Right now, the global annual cost of caring for patients with dementia has surpassed 1 trillion dollars [3]. The intolerable financial burden of care for patients with dementia and the unavailability of an effective treatment for postponing or stopping dementia progression has made it one of the most horrific diseases for the nations and families, while pharmaceutical advances of the illness have not been satisfying [3, 4].

Furthermore, until now, we have not completely comprehended the causes and etiology of the disease, which makes it more urgent to put dementia under the microscope. To cope with common difficulties caused by dementia, taking primary preventive measures such as adjusting modifiable risk factors, including cardiovascular diseases, obesity, diabetes, a sedentary lifestyle, and smoking is shown to be effective [5]. For example, a considerable drop in the rate of Alzheimer's disease in some countries has been attributed to an effective modulating of the preventable risk factors [6].

In the absence of modifiable risk factors, it becomes highly challenging to explain the possible risk factors responsible for the onset of the disease. Numerous studies

have already reported a broad range of risk factors for dementia. However, given the geographical differences in dementia prevalence and incidence, there is no comprehensive domestic study evaluating the possible risk factors for dementia in the Iranian population. Given the considerable differences between the culture and lifestyles of the Iranian community and other countries in the world, validating the findings of other parts of the world in the Iranian population is a highly demanding task. Therefore, this study aimed at providing a synoptic account of the possible medical and health-related risk factors associated with prevalent dementia. The presence of hospital information system, which makes it easy to access medical history information for retirees and staff members of the National Iranian Oil Company (NIOC) and more than 3 decades of the researchers' work in both operational and managerial positions makes NIOC an ideal place to conduct such studies.

Study population

The subjects were assessed and allocated to one of the following categories:

1) Cases: 180 patients with dementia (using the Diagnostic and Statistical Manual of Mental Disorders, fifth edition criteria, neurologist examination, paraclinical assessments, and brain imaging).

2) Controls: 371 individuals without dementia (The Mini-Mental State Examination cut-off point of >19 for illiterate or low-educated individuals, >27 for individuals having average educational attainment, and >29 for those having an academic educational achievement).

The sample size was calculated, using a power of at least 0.90 and detected an Odds Ratio (OR) of 2; the results revealed that 180 patients were necessary for the case group and 371 for the control group.

Setting

Axiomatically, the inclusion criteria for both the cases and controls were as follow: 1) being 60 years old or older, 2) being the staff member of NIOC with the petroleum industry health insurance coverage, 3) signing the informed consent form to participate in the study.

Selection of patients

All patients from 15 operational areas across the NIOC branches throughout the country referring to the hospitals and health centers of the NIOC or the neurologists working with NIOC in 2017 were included in the present study.

Selection of controls

The controls included proxies or close relatives of the dementia cases, who had no sign of cognitive problems and were visited by the physician or neurologist at the same time as the cases were.

2. Methods

Our strategy for extracting medical risk factors consisted of several phases. In the first phase, we conducted an electronic search on the PubMed and Web of Science databases from their start to January 2017 with the keywords “dementia” OR “Alzheimer” and “risk factor”; relevant primary and reviewed articles were revealed. Next, we scrutinized their abstracts for their relevance. We included articles focusing on fluid biomarkers or genetic factors as well. A factor would be considered a “risk factor” if it had shown a significant link to dementia in studies. If an association was covered by more than one study, we would keep the one with the strongest association with dementia. Articles related to the results other than dementia such as cognitive decline or impairment were excluded. This phase resulted in a list of 38 risk factors for dementia.

In the second phase, a panel of experts, including psychologists, neurologists, geriatrics, and gerontologists reviewed and assessed the items of checklist for the appropriateness and relevance of the items to dementia. The comments of the experts were used to revise and adjust the list. The comments of experts resulted in the

omission of some risk factors such as the ones related to cerebrospinal fluids because of their inapplicability.

In the third phase, the list was pretested on a sample of 30 older adults, which was not included in the final sample, to examine its usefulness and to include information about aspects of the patient’s personal life and demographic information. This resulted in the shortening of the list to 21 risk factors and sociodemographic information (Table 2).

In the final phase, the existence of medical risk factors was investigated by referring to the hospital information system of NIOC health centers, which is available since about 2 decades ago and is the archive for frequent routine medical evaluations for the staff and retirees. In this phase, the investigators were blinded to the aims of the research to avoid information bias.

Statistical analyses

The data were analyzed, using SPSS version 22 and STATA version 12. We described the quantitative and qualitative data as mean (standard deviation) and frequency (percentage). We assessed the associations of possible risk factors, using simple and multiple logistic regression. Furthermore, we evaluated the independent effects of the reproductive variables after adjusting for potential confounding variables, including age, marital status, and education using a multiple logistic regression model and the backward selection method. We summarized the results regarding adjusted and unadjusted odds (95% CIs) (Table 2).

3. Results

The participation rates of the cases and controls were 95% and 91%, respectively. The majority of the participants were male (55%), married (69%), with a Mean±SD age of 73.14±9.11, and with high school education (38%). Table 1 summarizes the demographic characteristics of the subjects.

As it is presented in Table 2, the univariate logistic regression demonstrated that a history of all the medical problems under assessment had significantly increased the chances of dementia. However, because of the high number of variables, we did not include insignificant variables such as homocysteine deficiency, history of high blood lipids, and open-heart operation in Table 2.

Table 3 presents the results of multiple logistic regression after adjusting for age, sex, and education. A

Table 1. Demographic characteristics of the cases and controls

Variable	Category	Cases (%)	Controls (%)
Age	60-74	65 (36.11)	229 (61.72)
	75-89	94 (52.22)	69 (18.59)
	90≥	21 (11.66)	3 (0.8)
Sex	Male	95 (52.77)	207 (55.79)
	Female	85 (47.22)	164 (44.20)
Education	Illiterate	27 (15)	22 (5.92)
	Elementary	58 (32.22)	53 (14.28)
	High school and diploma	68 (37.77)	139 (37.46)
	Associate diploma and bachelor's	21 (11.66)	135 (36.38)
	Master's and higher	6 (3.33)	22 (5.9)

Iranian Rehabilitation Journal

history of cancer (OR=15.31, $P<0.001$) and chronic anemia (OR=5.95, $P<0.001$) had significantly increased the chances of dementia. Moreover, a history of less (OR=7.50, $P<0.001$) and more than (OR=4.73, $P<0.001$) 1 year of vitamin D3 deficiency had also significantly increased the risk of dementia for the individuals.

4. Discussion

In the present study, we evaluated the association between dementia and medical risk factors. Although previous studies have reported different risk factors for dementia, but as far as we know, it is the first time that the risk factors for prevalent dementia in NIOC population are under microscope; it would not be unfair to assert that it is the first time that this kind of study is done in the Iranian population. Among the assessed risk factors, only a history of vitamin D, cancer, and chronic anemia showed a significant relationship with an increased chance of dementia.

Consistent with the results of previous studies, the results of this study showed that both less and more than 1 year of vitamin D deficiency have significantly increased the risk of dementia for the individuals. In a 30-year follow-up study, Afzal et al. have shown that vitamin D deficiency was strongly associated with an increased risk of dementia [7]. Similarly, other studies reported similar findings [8, 9]. Some explanations are proposed for the link between dementia and vitamin D deficiency. For

example, studies have linked vitamin D deficiency to cerebrovascular pathology, meaning that the deficiency escalates the risk of incident ischemic stroke through the increased number of large vessel infarcts, which in turn, have shown to increase the risk of dementia [5, 10, 11]. Another possible mechanism is that vitamin D receptors in the hippocampus and dentate gyrus are involved in learning and memory.

Similarly, the enzyme responsible for synthesizing 1,25-dihydroxy-vitamin D3 (the active form of vitamin D) is produced in several parts of the brain. The active version of vitamin D is responsible for regulating the expression of nerve growth factor and other factors of neurotrophic expression, as well as the life of neural cells [7]. In laboratory conditions, vitamin D stimulates phagocytic cells, which increases the removal of Beta-amyloid plaques, an indication of Alzheimer's disease [12]. A previous study showed that the inflammatory process of Alzheimer's disease is dependent on the pathway receptor-disturbance of vitamin D [12].

It is also established that vitamin D reduces cytotoxicity caused by amyloid and apoptosis in embryonic cortical neurons [13]. The inflammatory process of Alzheimer's disease is shown to be dependent on the pathway receptor-disturbance of vitamin D [14]. In animal experiments, vitamin D therapy has been shown to improve the decline in memory and learning caused by age [15]. In summary, both vascular and neurodegenerative

Table 2. Unadjusted odds ratios for medical risk factors and dementia in simple logistic regression

Risk Factors	Cases (%)	Controls (%)	Unadjusted Odds	95%CI	P	
A family history of Alzheimer's	29 (16.11)	30 (8)	2.18	1.26-3.76	0.005	
A family history of Parkinson	26 (14.44)	25 (6.7)	2.39	1.33-4.28	0.003	
Hypothyroid history	28 (15.55)	31 (8.35)	2.13	1.23-3.68	0.007	
Chronic vitamin B12 deficiency	86 (47.77)	41 (11)	7.93	5.10-12.32	<0.001	
Chronic folate deficiency	64 (35.55)	34 (9.16)	5.73	3.58-9.15	<0.001	
Head trauma history (significant. repeated)	34 (18.88)	16 (4.31)	5.33	2.85-9.97	<0.001	
Long-standing Estrogen deficiency	36 (20)	33 (8.89)	2.71	1.62-4.53	<0.001	
Cancer history	23 (12.77)	10 (2.69)	5.54	2.57-11.92	<0.001	
Chronic pain	72 (40)	73 (19.67)	2.90	1.95-4.31	<0.001	
Polypharmacy (5≥)	139 (77.22)	184 (49.59)	3.92	2.58-5.96	<0.001	
Chronic high blood-pressure	115(63.88)	188(50.67)	1.84	1.27-2.67	<0.001	
Type 2 diabetes	69 (38.33)	99 (26.68)	1.83	1.25-2.68	0.002	
Chronic anemia	93 (61.66)	29 (7.81)	13.76	8.48-22.31	<0.001	
Stroke	48 (26.66)	5 (1.34)	28.25	11-72.57	<0.001	
Chronic vitamin D deficiency	<1 year	93 (51.66)	47 (12.66)	9.49	6.07-14.76	<0.001
	>1year	19 (10.55)	31 (8.35)	2.94	1.55-5.55	
Chronic CVD	<5 years	29 (16.11)	38 (10.24)	2.52	1.47-4.31	<0.001
	>5 years	62 (34.44)	39 (10.51)	5.25	3.29-8.36	
Chronic eye problems	<1	36 (20)	39 (10.51)	2.57	1.55-4.28	<0.001
	>1	47 (26.11)	61 (16.44)	2.35	1.34-4.13	
Chronic digestion problems	<5 years	48 (26.66)	48 (12.93)	2.72	1.73-4.30	<0.001
	>5 years	21 (11.66)	20 (5.39)	2.86	1.49-5.48	
Chronic urinary problems	<5 years	57 (31.66)	51 (13.74)	4.12	2.63-6.47	<0.001
	>5 years	33(18.33)	15 (4)	8.12	4.21-15.68	
Chronic rheumatism or inflammation	<1 year	28 (15.55)	29 (7.81)	2.40	1.37-4.21	0.002
	>1year	26 (14.44)	46 (12.39)	1.40	0.83-2.38	
Chronic sleep disorders	<1 year	33 (18.33)	41 (11)	7.51	4.03-13.99	<0.001
	>1year	108 (60)	104 (28)	11.5	6.64-19.91	

Iranian Rehabilitation Journal

Table 3. Adjusted odds ratios for medical risk factors and dementia in multiple logistic regression

Variables	Adjusted Odds (95%CI)	P-Value	
Cancer history	15.31 (4.26-55.06)	0.001	
Chronic anemia	5.95 (2.50-14.16)	0.001	
Vitamin D deficiency	<1 year	7.50 (3.31-16.99)	0.001
	>1year	4.73 (1.33-16.08)	0.016

Iranian Rehabilitation Journal

mechanisms have been proposed for the link between vitamin D deficiency and dementia. The results lend some support to the notion that vitamin D may have neuroprotective roles [16].

A surprising finding of the present study implies that individuals, who had less than 1 year of vitamin D deficiency history (OR=7.50, $P<0.001$), had a 2.77 point higher chance for dementia compared with those having more than 1 year of vitamin D3 deficiency history (OR=4.73, $P<0.001$). This finding puts forward the idea that there may be acute and chronic roles for vitamin D deficiency in dementia pathology. Although not mentioned in the previous studies, with the aid of speculation, it can be suggested that acute vitamin D deficiency brings individuals a higher risk of dementia since they do not see the situation as critical and, consequently, do not seek proper treatment; this is the time, when the compensatory mechanisms are less efficient. But, after 1 year, the retaliatory mechanisms start working correctly or individuals start taking medications and lessen their chance of getting dementia. However, further studies are required to be conducted to investigate this phenomenon.

In the present study, we found a significantly higher risk of dementia for individuals with a history of cancer (OR=15.31, $P<0.001$) compared to those without it. Limited studies in this regard have reported contradictory findings. For example, a meta-analysis of observational studies by Lopez et al. in 2014 showed a weird inverse association between Alzheimer's disease and cancer; they showed that patients with a history of cancer had 50% less risk of Alzheimer's disease [17]. Several studies have tried to explain the biological and molecular associations between low predisposition to one type of disease and protection against other diseases [18, 19].

Ming et al. have also reported a significant inverse relationship between hematologic malignancies, lung cancer, and colorectal cancer [20]. However, these associations are rife with partiality since one particular disease may reduce the life of the patients and may not allow them to live longer to experience another or because of the presence of one condition, the other may remain undiscovered. On the other hand, the results of the current study were consistent with a study by Frain et al., where prostate cancer survivors had a moderately higher risk for developing Alzheimer's disease [21].

Similarly, the results of a cross-sectional study by Heflin et al. suggested that patients with cancer were at a higher risk of cognitive problems in comparison with the ones not experiencing it [22]. A proposed mechanism for

the possible link between cancer history and dementia is that the "growth factor progranulin" (PGRN), which has multiple roles, is an extracellular regulatory protein regulating cell division, survival, and inflammation. The levels of PGRN, which are shown to have roles in neurobiology, often increase in cancers. An autosomal mutation in PGRN results in neuronal atrophy in the frontal and temporal lobes and a consequent frontotemporal lobar dementia [23].

The inconsistency observed in our study with previous studies concerning the relationship between cancer and dementia deserves some comments. The majority of the studies mentioned above are conducted in developed countries; the individuals with a cancer diagnosis have access to quality health services or more effective treatment for their condition, which in turn, may result in better health for the individuals and, consequently, less risk of dementia. However, in a less developed country such as Iran, where the health systems have space for more development, it seems that the same biological pathways for cancer increase the risk of dementia for the individuals.

Based on our results, a history of chronic anemia had significantly increased the risk of dementia (OR=5.95, $P<0.001$), which is consistent with the results of 3 previous studies in this regard. One research showed that in a 3-year follow-up in 1139 older adults, anemia was related to a 2-fold increase in the risk of developing dementia [24]. Another study showed that anemia was linked to a 60% increase in dementia risk for older adults [25]. The third study showed that anemia was related to a significant relative risk of 1.64 for dementia [26].

Even though the mechanisms for the relationship between anemia and dementia have not been clearly understood until now, our results gave some support to this relationship. However, some hypotheses have been developed to outline the mechanisms for this association. The first hypothesis assumes that anemia results in chronic brain hypoxia, which may increase the risk of dementia [24]. Another theory asserts that anemia caused by kidney disease may be related to dementia since, in addition to regulating red blood cell production, erythropoietin receptors in the brain seem to have a protective effect against stroke and hypoxia; also, lower erythropoietin levels may increase the risk of neuronal degeneration [27]. Because of the deficiency of micronutrients such as iron and vitamin B12, anemia may also be associated with cognitive impairment and dementia. The lack of iron may lead to cerebral hypoxia and cogni-

tive decline because it plays a vital role in oxygen transport and storage in the brain [28].

The present study has several strengths, contrary to the other domestic studies on dementia, where dementia diagnoses have mostly been based on questionnaires or the reports of informants; we used the Diagnostic and Statistical Manual of Mental Disorders, fifth edition criteria, as well as neurologist's examinations, to confirm the presence of dementia. Moreover, this was the first domestic structured case-control study conducted in NIOC retirees for assessing the most common medical risk factors for dementia. Finally, because of the relatively big sample size of the present study and the existence of the similar reliable statistics for the elderly population in NIOC compared to the whole country according to Iranian national statistics (www.amar.org.ir), the results of this study can be easily validated by other populations.

Unfortunately, the information collected by the questionnaires was prone to recall bias. What is more, because of the nature of the research, we could not calculate the relative risk for medical and health-related exposures.

5. Conclusion

To recapitulate what we outlined above, the study proposed that vitamin D deficiency, cancer, and chronic anemia increased the risk of dementia in the NIOC retirees. However, the relationship between dementia and risk factors seems to be more complex than what we report here. A complicated interaction among medical, genetic, environmental, and sociodemographic risk factors, as well as the biology of the human body, makes it more urgent to design more casual studies. Finally, since most of the medical and health-related risk factors for dementia are potentially modifiable, preventing, controlling, and monitoring them seem to provide an excellent opportunity for policymakers to better address dementia as a public health priority.

Ethical Considerations

Compliance with ethical guidelines

The proposal of the present study was approved by the University of Social Welfare and Rehabilitation Sciences with the code of ethics: IR.USWR.REC.1396.414

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Authors' contributions

All authors contributed in preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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