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RISK FACTORS FOR AGE-RELATED DEMENTIA IN KAZAKHSTAN: A CASE-CONTROL STUDY

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Abstract

To our knowledge, no population-based studies have been conducted on dementia in Kazakhstan yet. The aim of our pilot research was evaluation of the risk factors of Alzheimer's disease and vascular dementia in Kazakhstani settings. 79 patients of dementia (37 males and 42 females) and 121 healthy controls (50 males and 71 females) were included in the study. Among 79 dementia cases 45 (57%) had Alzheimer's dementia, 34 (43%) vascular dementia. Dementia patients varied in age from 50 to 85 years, with a mean of 67.5 ± SD 8.3 years. There were 42 (53%) females and 37 (47%) males. A logistic regression analysis was employed to calculate odds ratios (OR) and corresponding 95% confidence intervals (CI) for potential factors associated with dementia. In our cohort, a significant risk factor for AD and VD was a nearly childhood in rural areas and small towns, whereas obtaining at least secondary education had protective effect on vascular dementia. Surprisingly, higher body mass index, having history of heart disease, high blood pressure and stroke had negative association with Alzheimer's dementia. These findings may be useful for facilitating advanced research on dementia and developing prevention plan of age-related dementias in Kazakhstan.

Key words: *Alzheimer's disease, vascular dementia, risk factors.*

Резюме

ФАКТОРЫ РИСКА РАЗВИТИЯ ВОЗРАСТНОЙ ДЕМЕНЦИИ В КАЗАХСТАНЕ: ИССЛЕДОВАНИЕ ПО ТИПУ СЛУЧАЙ-КОНТРОЛЬ

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Насколько нам известно, популяционных исследований деменции в Казахстане еще не проводилось. Целью нашего пилотного исследования была оценка факторов риска болезни Альцгеймера и сосудистой деменции в Казахстане. В исследование были включены 79 пациентов с деменцией (37 мужчин и 42 женщины) и 121 здоровый контроль (50 мужчин и 71 женщина). Из 79 случаев деменции 45 (57%) страдали деменцией Альцгеймера, 34 (43%) - сосудистой деменцией. Возраст пациентов с деменцией варьировался от 50 до 85 лет, в среднем 67,5 ± SD 8,3 года. Женщин было 42 (53%), мужчин - 37 (47%). Анализ логистической регрессии был использован для расчета отношения шансов (ОШ) и соответствующих 95% доверительных интервалов (ДИ) для возможных факторов, связанных с деменцией. В нашей когорте значительным фактором риска для болезни Альцгеймера и сосудистой деменции было детство в сельской местности и небольших городах, тогда как наличие хотя бы среднего образования имело защитный эффект от сосудистой деменции. Удивительно, но более высокий индекс массы тела, наличие в анамнезе сердечных заболеваний, высокого кровяного давления и инсульта имели отрицательную связь с деменцией Альцгеймера. Эти результаты могут быть полезны для содействия продвинутым исследованиям деменции и разработки плана профилактики возрастной деменции в Казахстане.

Ключевые слова: *болезнь Альцгеймера, сосудистая деменция, факторы риска.*

Түйіндеме

ҚАЗАҚСТАНДАҒЫ ЖАСҚА БАЙЛАНЫСТЫ ДЕМЕНЦИЯНЫҢ ҚАУІП ФАКТОРЛАРЫ: ЖАҒДАЙДЫ БАҚЫЛАУ ЗЕРТТЕМЕСІ

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Біздің білуімізше Қазақстанда деменцияны популяциялық зерттеу әлі жүргізілген жоқ. Біздің пилоттық зерттеуіміздің мақсаты - Альцгеймер ауруы мен Қазақстандағы тамырлық деменцияның қауіп факторларын бағалау. Зерттеуге деменциямен ауыратын 79 науқас (37 ер және 42 әйел) және 121 денсаулықты бақылау (50 ер адам және 71 әйел) енгізілді. Деменцияның 79 жағдайының 45-і (57%) Альцгеймердің деменциясынан, 34 (43%) тамырлы деменциямен ауырды. Деменциясы бар науқастардың жасы 50-ден 85 жасқа дейін, орташа 67,5 ± SD 8,3 жас аралығында. Олардың арасында 42 әйел (53%), ерлер - 37 (47%) болды. Логистикалық регрессиялық талдау деменциямен байланысты ықтимал факторлар үшін коэффициенттердің коэффициентін және 95% сенімді аралықты есептеу үшін қолданылды. Біздің когортада ауылдық жерлерде және шағын қалаларда балалық шақ Альцгеймер ауруы мен тамырлық деменцияның маңызды факторы болды, ал кем дегенде орта білімі қан тамырларының деменциясына қарсы қорғаныс әсерін тигізді. Бір таңқаларлығы, дене салмағының жоғарылауы, жүрек ауруының тарихы, жоғары қан қысымы және инсульт Альцгеймердің деменциясына теріс байланысты болды. Бұл нәтижелер деменцияның дамыған зерттеулерін алға жылжытуға және Қазақстанда жасына байланысты деменцияның алдын алу жоспарын жасауға пайдалы болуы мүмкін.

Түйін сөздер: *Альцгеймер ауруы, тамырлы деменция, қауіп факторлары.*

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Background

Dementia is among fast growing pathologies in the world that is associated with age, and affects millions of people worldwide irrespective of gender, education or social background. Dementia is an overall term for a diverse category of syndromes characterized by decline in memory, cognitive function, and behavior. Researchers estimated that that approximately 60 to 80 percent of individuals with dementia have Alzheimer's disease (AD). The second common type of dementia is vascular dementia (VD), which occurs after a stroke and accounts for about 15 to 20% of dementia cases [1, 7, 14]. There is also a mixed type of dementia that resulted from combination of AD and cerebrovascular pathologies [14]. The less common types of dementias are frontotemporal dementia and dementia with Lewy bodies (accounts for less than 20% cases combined) [12]. However, dementia in low and middle-income countries remains under-researched and growing public health concern with societal impact. Little research, policy or practice is directed towards older adults [13].

Many risk factors have been recognized as contributors towards the development of dementia. These include both non-modifiable (age, gender, family history, genetic) and modifiable factors such as low education, midlife hypertension, smoking, high cholesterol, physical inactivity, obesity and diabetes and many others [12, 16]. However, little information is available about age-related dementia epidemiology in Central Asia, and no case–control study of risk factors for dementia in Kazakhstan has been conducted thus far.

The aim the present study was undertaken to evaluate the relative importance of various risk factors of age-related dementia in a population over 50 years old in Nur-Sultan city, Kazakhstan.

Materials and methods

We conducted a case–control study of age-related dementia in Nur-Sultan city. The screening process included finding possible dementia cases among elderly population of Nur-Sultan city. Those who were identified as subjects with possible dementia were clinically examined by experienced neurologists. We used a formalized questionnaire and specially designed assessment forms. The investigation included an extensive neurological and psychiatric examination, and a battery of neuropsychological tests to assess cognitive functions. The neuropsychological tests included the Mini-Mental State Examination (MMSE) and Clock-drawing test. Magnetic resonance imaging (MRI) scans were used whenever possible to exclude secondary causes of dementia (brain injuries, tumors, etc.). All informants (cases and controls) were asked about their demographic details (e.g. sex, age, social and marital status), presenting symptoms, medical and history of head trauma, smoking, alcohol consumption, previous medical conditions, existing chronic diseases. The same methodology was used to collect information in both cases and controls. Patients were considered to have a positive family history when there was at least one first-degree relative (parents, siblings) with dementia. Diagnosis of dementia was based on criteria described in the Diagnostic and Statistical Manual of Mental Disorders

(DSM-IV), and the diagnosis required impairment in short- or long-term memory and in one other cognitive domain, as well as a cognitive decline sufficiently severe to impair everyday social functioning, including the patient's ability to work and perform activities of daily living. Criteria for classification of AD were based on those developed by The National Institute of Neurological and Communicative Disorders (NINCDS) and Related Disorders Association (ADRDA) Work Group [7, 8]. Vascular dementia was diagnosed according to the DSM-IV. Other dementias (post-traumatic, depression, chronic intoxications, alcoholism, etc.) were excluded based on the medical history (including exposure to a particular drug), results of medical examination (e.g. temporal relation to dementia, presence of focal neurological symptoms, presence of associated medical conditions such as endocrine or neurological disorders, episodes of loss of consciousness, and behavioral changes).

A control group was selected from out-patient and in-patients departments of city clinics of the same catchment area of the cases in Nur-Sultan. We matched control group by sex and age. Demographic and risk factors data in controls were collected using the uniform structured questionnaires. MRI investigations of the head were not carried out in controls unless medically justified. Exclusion criteria for controls were: evidence of dementia or cognitive decline, psychiatric disorder, and alcohol/drug abuse. The study was approved by the Local Ethics Committee of Center for Life Sciences National Laboratory Astana, and informed consent to participate in the study was obtained from all participants or their caregiver (if the subject was severely demented) before the subjects were interviewed. The following information about risk factors was collected during structured interviews from all the cases and controls: smoking, frequency and amount of alcohol consumption, family history of dementia or cognitive decline, history of depression, head trauma with loss of consciousness, history of diabetes mellitus, hypertension, ischemic heart disease, etc. A logistic regression analysis was used to estimate associations between putative risk factors and dementia. Odds ratios (OR) with the corresponding 95% confidence intervals (CI) were calculated. One-way ANOVA or Kruskall-Wallis tests were used to compare continuous variables and Chi-squared test was used to find differences in the frequency of risk factors between cases and controls. Variables shown to be significant in the univariate analysis were entered in the multivariate model, adjusted for age and sex. The value of $p<0.05$ was considered to be the point of significance. All analyses were conducted using Stata 13 (NC, USA).

Results

A total of 79 dementia patients and 121 controls were enrolled in the study. Dementia patients varied in age from 50 to 85 years, with a mean of 67.5 ± SD 8.3 years. There were 42 (53%) females. Majority of the patients (75.5%) had university or college degree and 14.9% had secondary education. Among 79 dementia cases 45 (57%) had Alzheimer's dementia, 34 (43%) vascular dementia. As shown in the Table 1, body mass index (BMI) was lower among cases compared to controls; atherosclerotic index was the highest in patients with Alzheimer's disease, followed by vascular dementia cases.

Table 1.

Characteristics of cases and controls.

Variable	Controls n=121	Alzheimer's disease cases n=45	Vascular dementia cases n=34	p-value*
1	2	3	4	5
Age, mean ± SD	67.2±8.3	65.5±9.4	69.7±6.7	0.084
Body Mass Index, mean ±SD	27.7±4.8	24.1±2.6	25.8±2.5	<0.001
Atherosclerotic index, median (IQR)	2.5 (1.9-3.6)	3.2 (2.7-3.7)	3.15 (2.2-4.2)	0.033
Sex, (%)				0.275
Male	71 (58.7)	27 (60)	15 (44.1)	
Female	50 (41.3)	18 (40)	19 (55.9)	
Education, n (%)				0.001
None	13 (10.7)	4 (8.9)	6 (17.6)	
Secondary	42 (34.7)	4 (8.9)	4 (11.8)	
College or university	66 (54.6)	37 (82.2)	24 (70.6)	
Place of birth, n (%)				<0.001
City	43 (35.5)	4 (8.9)	4 (11.8)	
Town	40 (33.1)	14 (31.1)	10 (29.4)	
Rural area	38 (31.4)	22 (60)	20 (58.8)	
Heart problems, n (%)				0.019
No	74 (61.2)	37 (82.2)	19 (55.9)	
Yes	47 (38.8)	8 (17.8)	15 (44.1)	
High blood pressure, n (%)				<0.001
No	38 (31.4)	28 (62.2)	6 (17.6)	
Yes	83 (68.6)	17 (37.8)	28 (82.4)	
Stroke, n (%)				<0.001
No	91 (75.2)	42 (93.3)	15 (44.1)	
Yes	30 (24.8)	3 (6.7)	19 (55.9)	

Continuation Table 1.

1		2	3	4	5
Transient ischemic attack, n (%)					0.275
	No	94 (77.7)	40 (88.9)	27 (79.4)	
	Yes	27 (22.3)	5 (11.1)	7 (20.6)	
Brain injury, n (%)					0.353
	No	110 (90.9)	41 (91.1)	28 (82.3)	
	Yes	11 (9.1)	4 (8.9)	6 (17.7)	
Diabetes mellitus, n (%)					0.205
	No	107 (88.4)	39 (86.7)	26 (76.5)	
	Yes	14 (11.6)	6 (13.3)	8 (23.5)	
Depression, n (%)					0.357
	No	105 (86.8)	35 (77.8)	28 (82.4)	
	Yes	16 (13.2)	10 (22.2)	6 (17.6)	
Family history of dementia, n (%)					0.192
	No	116 (95.9)	40 (88.9)	31 (91.2)	
	Yes	5 (4.1)	5 (11.1)	3 (8.8)	
Smoking history, n (%)					0.065
	No	100 (82.6)	33 (73.3)	22 (64.7)	
	Yes	21 (17.4)	12 (26.7)	12 (35.3)	
Heavy drinking history, n (%)					0.565
	No	110 (90.9)	41 (91.1)	29 (85.3)	
	Yes	11 (9.1)	4 (8.9)	5 (14.7)	

*Note: *controls were compared to Alzheimer's dementia and vascular dementia*

The majority of cases with AD and VD were born in rural areas. Having high blood pressure in medical history was observed in VD cases mostly. Although having family history of dementia among first-degree relatives (mother, father and siblings) was more prevalent among AD cases, analysis did not reveal statistical significance. Univariate logistic regression analyses (Table 2) revealed that higher body mass index, having history of heart disease, high blood pressure and stroke had negative association with Alzheimer's dementia, whereas negative association with the risk of VD observed with having secondary education compared to none. Place of birth was strongly associated with the risk of AD and VD, where cases born in rural area had 7.63 fold increase in odds of having AD and 5.65 fold increase in having VD compared to being born in urban area. After adjusting for age and gender the above-mentioned risk factors remained significant and shown in the Table 3.

Table 2.

Univariate analysis of risk factors for AD and VD.

Risk factor	Alzheimer's dementia OR (95% CI)	*p-value	Vascular dementia OR (95% CI)	*p-value
1	2	3	4	5
BMI	0.75 (0.64-0.87)	<0.001	0.88 (0.76-1.02)	0.106
Atherosclerotic index	1.12 (0.85-1.5)	0.408	1.2 (0.95-	0.109
Education (reference= no education)				
Secondary	0.3 (0.07-1.41)	0.130	0.2 (0.05-0.84)	0.028
College or university	1.82 (0.55-5.99)	0.323	0.78 (0.26-2.3)	0.664
Place of birth (reference = city)				
Town	3.76 (1.14 – 12.4)	0.029	2.68 (0.78-9.25)	0.117
Rural area	7.63 (2.44 – 23.8)	<0.001	5.65 (1.77-18.02)	0.003
Heart problems (reference = no)	0.34 (0.14– 0.79)	0.013	1.24 (0.57-2.68)	0.579
High blood pressure (reference = no)	0.27 (0.13 -0.56)	<0.001	2.13 (0.81-5.58)	0.122
Stroke (reference = no)	0.21 (0.06-0.75)	0.016	3.84 (1.73-8.48)	0.001
Transient ischemic attack (reference = no)	0.43 (0.15-1.2)	0.111	0.9 (0.35-2.29)	0.830
Brain injury (reference = no)	0.97 (0.29-3.23)	0.968	2.14 (0.72-6.29)	0.166
Diabetes mellitus (reference = no)	1.17 (0.42-3.27)	0.757	2.35 (0.89-6.19)	0.084
Depression (reference = no)	1.87 (0.77-4.5)	0.160	1.4 (0.5-3.92)	0.515
Family history of dementia (reference = no)	2.9 (0.79-10.54)	0.106	2.24 (0.5-9.91)	0.286
Smoking history (reference = no)	1.73 (0.76-3.89)	0.185	2.59 (1.11-6.05)	0.027
Heavy drinking history (reference = no)	0.97 (0.29-3.23)	0.968	1.72 (0.55-5.35)	0.346

*Note: * compared to controls*

Table 3.

Multivariate analysis of risk factors for AD and VD.

Risk factor	Alzheimer's dementia OR (95% CI)	*p-value	Vascular dementia OR (95% CI)	*p-value
1	2	3	4	5
BMI	0.74 (0.63-0.87)	<0.001	0.88 (0.75-1.02)	0.108
Education (reference= no education)				
Secondary	0.13 (0.68-1.44)	0.137	0.2 (0.48-0.86)	0.032
College or university	1.92 (0.54- 6.7)	0.307	1.19	0.773
Place of birth (reference = city)				
Town	3.87 (1.16-12.88)	0.027	2.43 (0.69-8.47)	0.163
Rural area	9.78 (3.0-31.89)	<0.001	5.31 (1.56-18.01)	0.007
Heart problems (reference = no)	0.33 (0.13-0.83)	0.019	1.12 (0.47-2.66)	0.793
High blood pressure (reference = no)	0.28 (0.13-0.59)	0.001	1.75 (0.64-4.79)	0.273
Stroke (reference = no)	0.22 (0.06-0.80)	0.021	3.35 (1.48 -7.59)	0.004
Smoking history (reference = no)	1.92 (0.8 -4.62)	0.141	2.32 (0.91-5.92)	0.076

*Note: * compared to controls*

Discussion

This is the first study of dementia risk factors in Kazakhstani population. It is well known that AD and VD share common risk factors, pathogenesis, and clinical features [10]. The common risk factors include advanced age, sex, genetic factors, vascular factors, such as high blood pressure, diabetes, diet, metabolic syndrome, high cholesterol, stroke, physical inactivity peripheral and etc [12, 16].

In a given study we found that BMI was inversely associated with AD. Previous studies suggest that the association between BMI and dementia can be attributed by either a direct negative effect of excessive body weight on dementia development or reverse causation as a result of weight loss during the preclinical dementia stage [6]. In current study patients in dementia group had lower BMI compared to controls without cognitive impairment, however, it is unknown if the weight loss occurred before the onset of dementia symptoms, since midlife weight of the participants was not recorded.

Prospective epidemiological data demonstrated that vascular risk factors present in midlife, including (but not limited to) hypertension, diabetes and hyperlipidemia are associated with a clinical diagnosis of AD later in life. According many epidemiological studies hypertension in middle age significantly elevates the risk of cognitive decline in older age. Studies suggests that possible pathological mechanism can be affected by structural and functional impairment of the cerebral blood vessels, as well as by direct impact on the functions of the central nervous system through changes in the cerebral renin–angiotensin system [17]. In this regards, our results might seem paradoxical as elevated blood pressure is well-established vascular risk factor for Alzheimer's dementia. Nevertheless, some studies show inverse association between hypertension and cognition such as all-cause dementia, mixed AD/VD, and AD [4]. Moreover, Mendelian randomization study of AD using single-nucleotide polymorphism (SNP) revealed that higher blood pressure was associated with lower risk of AD [11]. In our study, the history of potential modifiable risk factors was recorded from participant's survey and did not differentiate by the time of dementia onset. Thus, it's possible that inaccurate information may have been recorded because of recall bias. We did not account for use of antihypertensive drugs as well, which also may alter the causal relationship between hypertension and AD risk. Despite increased recognition of the role of vascular factors in dementia we did not find significant association between having hypertension, stroke and heart diseases in medical history and risk of VD in our study.

Systematic review and meta-analysis of geographical variations of dementia worldwide concludes that rural living is associated with an increased risk of Alzheimer disease; the early life rural living further increases this risk [15].Studies examining early-life risk factors for dementia and cognitive impairment in later life suggest that individuals with low degree of education and residing in rural settings in childhood had a particularly high risk of dementia compared with those living in urban area in childhood. This might be explained by the fact that children in rural areas can be more engaged in housework than studying [18]. This evidence supports finding from our study where early life in rural or small town settings had a dramatic increase of odds of developing AD and VD.

Although heavy drinking is known to be a considerable risk factor for dementia [5], we did not find an association in our cohort of dementia patients. This might be explained by the fact that alcohol-related cognitive impairments were exclusion criteria in our study.

We did not observe a significant association between dementia and diabetes, despite the fact that studies suggests that diabetes is a risk factor both for VD and AD, in which it represents a form of diabetes that selectively involves the brain [2, 3].

The strength of this study is that we used international criteria for differential diagnosis of dementia and validated instruments for neuropsychological assessments and socio-demographic data collection, which enables cross-cultural comparison with different countries. Moreover, this is the first formal study of dementia risk factors and results of our study can provide background information for future dementia studies in Kazakhstan.

However, there are several limitations in our study. We used hospital-based cohort for cases selection, where avoidance of selection and survival biases is challenging, and inference of the study results on general population is limited. In fact, patients with more advanced stages of

dementia, with underlying conditions were more likely to be admitted to healthcare facilities, thus, underrepresenting individuals with mild dementia. Nevertheless, we believe that associations found in the study did not significantly alter from previously reported case-control studies on risk factors in other countries. Another limitation of the study is a small sample size of cases. Therefore, the lack of significant association between some predictors and dementias might also be due to limited statistical power of the study. Nevertheless, this is the first pilot study of risk factors for age-related dementia in Kazakhstan that provides background information for more advanced studies for better understanding of the etiology of dementias in the local settings.

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Contribution

Aiym Kaiyrlykyzy - drafted manuscript, conducted data analysis, provided results and discussion,

Andrey Tsoy, Farkhad Olzhayev, Dinara Alzhanova, Alma Zhussupova - conducted data collection and data cleaning,

Sholpan Askarova - devised the project, the main conceptual ideas and proof outline.

All authors discussed the results and commented on the manuscript.

The authors declare ***no conflicts of interest***.

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