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Original Article

Association of Diabetes Mellitus Type 2 and Alzheimer's Disease

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ABSTRACT

Background: Insulin serves an important role in brain metabolism, and insulin resistance and subsequent diabetes mellitus type 2 (DM2) can give rise to dysfunction of brain metabolism. This study aimed to test the hypothesis of association of late onset Alzheimer's disease (AD) with DM2 in an Iranian population.
Methods: In this case-control study, 243 subjects including 81 patients with late onset AD and 162 healthy controls were recruited. The frequency of DM were compared in AD patients with non-AD counterparts.
Results: The prevalence of diabetes in AD and control patients was 27% and 9%, respectively. (OR = 3.94, 95% confidence interval: 1.89-8.22). After adjustment for age and gender, there was a significant association between DM2 and AD (OR = 3.7, 95% confidence interval: 1.73-8.00).
Conclusion: The evidence from the present study suggested that DM2 was associated with AD in an Iranian population. Further longitudinal studies are warranted to confirm this finding.
Keywords: Alzheimer's disease, Brain metabolism, Diabetes mellitus type 2, Insulin resistance
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Introduction

Alzheimer's disease (AD) is a neurodegenerative disease affecting memory, thinking, and behavior. AD accounts for 60-70 percent of all type of dementias (1). AD is subdivided into early- and late-onset according to age of onset of 65 years. To date, there has been no treatment for stopping or reversing progression of the disease. The cause of AD is not well understood, however, several genes have been found to be associated with the disease (2). Accumulation of extracellular Beta amyloid plaques and intracellular hyperphosphorylated tau tangles are crucial molecular events in brain of AD patients. Diabetes mellitus arises from impaired insulin production (Diabetes Mellitus type 1 [DM1]) or lack of response to existing insulin (Diabetes Mellitus type 2 [DM2]). Not only is insulin secreted in the peripheral systems, but also it is released in the brain. The brain insulin and that transmitting through blood brain barrier play crucial roles in metabolism, neuroendocrine function, and

neuromodulation. Hyperglycemia can result in mitochondrial dysfunction (3). In addition, oxidative stress, insulin resistance, and cognitive dysfunction have been demonstrated in DM2 (4). DM2 increases with age and affect multiple organs such as brain. It has also been demonstrated that insulin resistance is associated with Beta amyloid plaques, hyperphosporylated tau tangles, reactive oxygen species, and neuroimflamation (5). Experimental studies have shown that brain diabetes shares many features with AD. Genetic factors have a role in both AD (6) and DM2 (7, 8). More recently, it has been suggested that AD can be a metabolic disorder with biochemical and molecular characteristics associated with DM2 (9). A role for insulin resistance in the pathobiology of AD has also been proposed. Epidemiological studies in various ethnicities have produced contradictory findings regarding association of DM2 and AD (10-12). Moreover, to the best of our knowledge, no investigation has been carried out on such an association in Iranian population. The present case-control study was designed to test the hypothesis of association of DM2 with susceptibility to AD in an Iranian population to provide basis for future cohort studies.

Methods

In the present case-control study, 243 subjects including 81 patients with AD and 162 controls were studied. The patients were recruited from educational and therapeutic centers of Guilan University of Medical Sciences, Rasht, Iran. The case group were selected from newly diagnosed late onset AD patients. AD patients were defined as possible and probable diagnosis of AD based on clinical examination, neuropsychiatric tests, and MRI criteria of the National Institute on Aging-Alzheimer's Association workgroups (13). Late onset AD patients was defined as AD with onset of the disease at or after the age of 65 years. Hospital controls were selected from patients in orthopedic surgery unit. Patients with a history of hypertension, stroke, motor neuron diseases, hereditary dementia disease, neuro-infection, neuropsychiatric systemic lupus erythematosus, neurosarcoidosis, multiple sclerosis, any other neurodegenerative disease were excluded from the study. The patients were investigated for demographic information including age and gender. DM2 was assessed according to self-report, medical record of physician diagnosed DM2, or use of glucose lowering medication. Data were analyzed using chi-squared tests. Odds ratio (OR) with 95% confidence interval (CI) were calculated using logistic regression model in SPSS software version 23. A P-value less than 0.05 was considered statistically significant.

Results

In total, 243 subjects including 81 patients with AD and 162 controls were assessed. The mean age of patients in the case and control group were 76.7 ± 8.2 and 75.9 ± 8.1 years, respectively (P-value = 0.43). There was no significant difference in age and gender between the two groups. Females accounted for 55.5 % and 46.2 % of the subjects in the AD and the control groups, respectively; notwithstanding 45.5 % and 64.8 % of the male subjects in the Alzheimer's and the control groups, respectively. Univariate logistic regression analysis showed significant association between DM2 and AD (P-value $\leq$ 0.001). After adjustment for age, there was still a significant association between DM2 and AD (P-value = 0.001). Table 1 summarizes analyses of association of gender and DM2 with AD.

Discussion

To the best of our knowledge, no study has investigated the role of DM2 in dementia including AD in Iran. Findings of the present study indicated that DM2 is associated with AD. This association was also significant after adjustment for age and gender. Neuroimaging studies have shown that clinical features of AD patients associated with DM may differ based on brain imaging pattern (14). Association of DM2 and AD has been a subject of research interest in various populations. There is growing evidence indicating the role of insulin resistance in AD. A systematic review studying association of DM2 and AD has reported risk ratios of greater than one in all the studied publications (15). In a retrospective review of an American cohort study (16), diagnosis of AD based on amyloid biomarkers from cerebrospinal fluid (CSF) and PIB-PET (positron emission tomography) and FDG-PET, MRI, and CSF tau, DM2 was significantly more prevalent in the AD patients than in the controls (16).

This result was in agreement with findings of our study as we found that 27 % of the patients with AD had DM2, in contrast to 9% of the control subjects with DM2. Elsewhere, a population-based cohort of 2574 Japanese-American subjects showed that DM2 was associated with total dementia diagnosed using clinical examination and MRI (RR = 1.5, 95% CI = 1.01-2.2), AD (RR = 1.8, [95% CI = 1.1-2.9]), and vascular dementia (RR = 2.3, 95% CI = 1.1-5.0) (10). Arvanitakis et al. carried out a cohort of 824 nuns older than 55 years for up to 8 years and found that in a proportional hazards model adjusted for education, gender, and age, DM nuns experienced a 65% increase risk of developing AD (assessed by clinical examination, neuropsychiatric tests, and imaging where available), in comparison with nuns without DM (HR = 1.65, 95% CI = 1.10-2.47) (11). In contrast, Akomolafe et al. (17) in a cohort of American population using criteria of National Institute of Neurological and Communicative Diseases and Al Emam (18) in cohort Egyptian study reported no significant association between DM and AD.

Table 1. Univariate and Multivariate Association of Alzheimer's Disease with Age, Sex, and Diabetes Mellitus

Variables	Alzheimer group	Control group	P-value	Unadjusted OR	95% CI	Adjusted OR	95% CI	P-value
Age in years, Mean (SD)	76.7 (8.2)	75.9 (8.1)	0.43	1.01	0.98-1.04	1.01	0.97-1.04	0.46
Gender								
Female	45 (55.5)	75 (46.2)	0.17	0.69	0.40-1.17	0.87	0.49-1.55	0.64
Male	36 (45.5)	87 (64.0)						
Diabetes mellitus type 2	22 (27)	14 (9)	0.001	3.94	1.89-8.22	3.73	1.73-8.00	0.001

Abbreviation: SD, standard deviation; OR, odds ratio; CI, confidence interval. Values are frequency (percent) unless otherwise indicated

The association of DM with some other nourdegetrative disorders including vascular cognitive impairment and vascular dementia has also been reported in a number of studies (12,19-21). In the present study we defined AD patients as possible and probable diagnosis based on clinical examination, neuropsychiatric tests, and MRI; however, studies based upon autopsy and functional neuroimaging including PET with FDG and PIB provide more precise diagnosis. Diabetes and insulin resistance mediate neurodegeneration through several mechanisms in AD. Insulin resistance increase activity of kinase enzyme which phosphorylate tau proteins, accumulation of beta amyloid plaques, oxidative and endoplasmic reticulum stress, production of reactive oxidative and nitrogen species, mitochondrial dysfunction, and signaling by pro-apoptosis and pro-inflammatory cascades (24-26).

Our study has merits and demerits. To the best of knowledge, our study is the first evaluation of DM2 in Iranian AD and control subjects, investigating association of DM2 and AD in the population. Another advantage of our study is the inclusion of only late onset AD and carrying out age matching of the control subjects with AD subjects. Nevertheless, a drawback of our study is its case-control design, compared to prospective cohort design performed in other similar studies. In addition, an important limitation of case-control studies of this type is measurement bias arising from evaluation of clinical records. To minimize possible prevalence bias in the case-control investigation, we recruited newly onset AD to strengthen the temporal association between AD and previous diagnosis of DM. Other demerit of the present study is lack of measurement of parameters such as genetic factors, education level, smoking status, alcohol consumption, metabolic syndrome, and duration and severity of DM2. An intrinsic limitation of all of AD studies is the definite diagnosis of AD based on brain autopsy. However, we should not ignore the salient fact that such a novel case-control AD-DM2 study in an Iranian population provides insights for future investigations.

Conclusion

The findings of the present study indicate that DM2 is associated with higher risk of AD in the studied Iranian population. A prospective study design investigating several risk factors would be beneficial to future studies.

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Ethical consideration

The present study was approved by research ethics committee of Guilan University of Medical Sciences (IR.GUMS.REC.1397.523).

Conflicts of interests

Authors declared no conflict of interest.

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