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RESEARCH

VITAMIN D IS ASSOCIATED WITH COGNITIVE STATUS IN PATIENTS WITH ALZHEIMER'S DISEASE

Abstract

Introduction: Previous studies have reported an association between low 25-hydroxyvitamin D (25(OH)D) levels and cognitive impairment. However, this association has not been reported in Turkish patients with cognitive impairment. We investigated this relationship in Turkish patients diagnosed with Alzheimer's disease (AD).

Materials and Method: Seventy-two patients with a diagnosis of "Probable AD" were included in the study. Demographic and disease specific characteristics were recorded. Cognitive performance was assessed using the Mini-mental State Examination (MMSE). Patients were categorized into two groups with regard to their 25(OH)D levels based on the recommended cut-off value (30 ng/ml) for 25(OH)D insufficiency. Association between 25(OH) D levels and MMSE scores was assessed using a regression model taking probable confounding factors into account.

Results: Sixty-nine patients were included in the final analysis. Patients with 25(OH)D levels higher than 30 ng/ml performed (n=18) significantly better in MMSE than the group with lower values (n=51) (p=0.027). Subsequently, the multiple linear regression analysis showed a significant association between 25(OH)D levels and MMSE scores; this association was independent of the confounding effects of age, gender, education, disease duration, anti-dementia medication and depressive state (B= 2.81, p=0.04).

Conclusion: Our results support that low 25(OH)D levels are associated with worse cognitive performance in Turkish patients with AD. Larger population-based studies are required to clarify this relationship in Turkish population not only in patients with AD, but also in individuals with mild cognitive impairment and healthy elderly.

Keywords: Alzheimer disease; Vitamin D; Aged

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ARAŞTIRMA

ALZHEİMER HASTALIĞINDA VİTAMİN D'NİN KOGNİTİF DURUM İLE İLİŞKİSİ

Öz

Giriş: 25-hidroksivitamin D (25(OH)D) yetersizliğinin bilişsel bozuklukla ilişkili olduğu önceki çalışmalarda bildirilmiştir. Ancak bu ilişkiyi bilişsel işlevlerde yıkımı olan Türk Alzheimer hastaları örnekleminde inceleyen bir çalışmaya ulaşılabilen literatür bağlamında rastlanmamıştır. Bu çalışmada, Türkiye'de Alzheimer hastalığı (AH) tanısı almış hastalarda bu ilişkiyi araştırmak amaçlanmıştır.

Gereç ve Yöntem: Bu çalışmaya "Olası AH" tanısı almış 72 hasta dahil edilmiştir. Hastaların demografik ve hastalıkla ilişkili özellikleri kayıt altına alınmıştır. Bilişsel durum değerlendirmesi için Standardize Mini Mental Durum Testi (SMMDT), depresyon taraması için ise Geriatrik Depresyon Ölçeği (GDÖ) kullanılmıştır. Hastalar 25(OH)D yetersizliği için daha önce önerilmiş olan 30 ng/ml düzeyine göre iki gruba ayrılmıştır. 25(OH)D düzeyi ve SMMDT puanları arasındaki ilişki, regresyon modeli ile hastaların bilişsel performanslarına etki edebilecek olası diğer faktörler de göz önüne alınarak değerlendirilmiştir.

Bulgular: Toplamda 69 hasta analize alınmıştır. 25(OH)D düzeyi 30 ng/ml ve üzeri olan grup (n=18) SMMDT'nde düsük değerleri olan gruba oranla (n=51) anlamlı olarak daha başarılı performans göstermiştir (p=0.027). Bir sonraki aşamada uygulanan çoklu lineer regresyon analizi sonuçları, 25(OH)D düzeyi ile SMMDT puanları arasında yaş, cinsiyet, eğitim, hastalık süresi, tedavi ve depresif durumun etkilerinden bağımsız anlamlı bir ilişki olduğunu göstermistir. (B=2.81, p=0.04).

Sonuç: Elde edilen sonuçlar AH tanısı almış Türk hastalarda düşük 25(OH)D düzeyinin düşük bilişsel performans ile ilişkili olduğuna işaret etmektedir. Türk toplumunda bu ilişkiyi sadece AH'nda değil, hafif bilişsel bozukluğu olan kişilerde ve sağlıklı yaşlılarda da araştıracak geniş ölçekli toplum bazlı çalışmalara ihtiyaç vardır.

Anahtar sözcükler: Alzheimer hastalığı; Vitamin D; Yaşlı

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by decline in cognitive functions, especially loss of episodic memory (1,2). As the leading cause of dementia, the global prevalence of AD is estimated to quadruple over the following decades, reaching 115.4 million by 2050 (1), which is expected to have a huge socioeconomic impact. Despite considerable efforts, no treatment that could slow or alter the disease progression has yet been found. Thus, currently, detection and treatment of the modifiable causes of AD are of utmost importance.

Several modifiable medical or lifestyle risk factors for AD such as diabetes, hypertension, physical inactivity, poor education in the early phase of life and socioeconomic status have been reported in various studies (2). Following the improvement of these factors over the past decades a decline in the prevalence of AD was achieved especially in the developed countries (3). It has been reported that 25-hydroxyvitamin D (25(OH)D) insufficiency may also be one of these risk factors. Despite controversy, the majority of reports in literature including large population-based studies favor the association between low 25(OH)D levels and cognitive impairment (4).

A prevalence study has reported that 33% of the Turkish elderly population has 25(OH) D deficiency (5). However, to the best of our knowledge no study has evaluated the association between 25(OH)D levels and cognitive impairment in Turkish elderly individuals. Thus, in this study we set out to investigate this relationship in Turkish patients who were diagnosed with AD

MATERIALS AND METHOD

Patients and clinical assessments

Seventy-two patients who fulfilled the criteria for "probable AD with increased level of certainty" according to the latest diagnostic guideline (6) were recruited from the outpatient clinic of Department of Neurology between January and November 2018. Demographic and disease specific data including education, disease duration (based on symptom onset) as well as anti-dementia medication (Donepezil, Rivastigmine, Memantine) were collected. Depressive state was evaluated using the Turkish version of the Geriatric Depression Scale (GDS). Cognitive performance of the patients was assessed using the Turkish version of the Mini-mental State Examination (MMSE). Eleven patients were assessed by the Montreal Cognitive Assessment (MoCA) for whom the scores were converted to MMSE using the suggested conversion table (7). Based on the previously recommended cut-off value (30 ng/ml) for 25(OH)D insufficiency (8), the patients included in the study were categorized into two groups (25(OH)D levels ≥30 ng/ml and <30 ng/ml). All procedures were performed in accordance with the Declaration of Helsinki, and an informed written consent was obtained from all participants or legal representatives.

Biomaterial collection

Blood levels of 25(OH)D were analyzed using the standard operating procedure using high-performance liquid chromatography (Thermo-Finnigan, Waltham, US) along with the ClinRep HPLC 25(OH)D kit (RECIPE Chemicals & Instruments GmbH, Munich, Germany). Samples were injected in a mobile phase, which had a flow rate of 1.0 ml/min. To determine of the within-run precision, the samples were measured in duplicate. The estimated average coefficient of variation was 4.8%.

Statistical analyses

Descriptive and quantitative data are given as mean and standard deviation. Demographic data and the MMSE scores of the two groups were compared using student's t-test (for continuous variables) or a chi-square test (for categorical

variables). A multiple linear regression analysis was further performed to assess the association between 25(OH)D levels and the MMSE scores; age, sex, education, GDS, disease duration and anti-dementia medication were considered as covariates. A hierarchical entry method was used in which the covariates were added in the first step following the inclusion of 25(OH)D groups in the second step. The significance threshold was set to $p < 0.05$. SPSS Statistics 21.0 sofware package (SPSS Ltd., Chicago, IL, US) was used for the analysis.

RESULTS

Of the 72 patients recruited in the study, 3 patients were excluded due to missing 25(OH)D values. The remaining 69 patients were divided into two groups: patients with 25(OH)D levels ≥30 ng/ml (n=18) and <30 ng/ml (n=51). Age, sex, education, depressive state, disease duration or anti-dementia medications of the two groups were similar (Table-1). Student's t-test showed that regarding MMSE, the performance of patients with 25(OH)D levels ≥30 ng/ml was significantly better than that of those with levels <30 ng/ml (p=0.027).

Additionally, multiple linear regression was performed to predict the MMSE scores based on age, gender, education, GDS, disease duration, anti-dementia drug usage, and 25(OH)D groups. A significant regression equation was found ($F(7,60) = 5.345$; $p < 0.001$) in the first step with an R2 of 0.38. With the inclusion of 25(OH)D groups in the second step, the R2 value increased to 0.43 ($F(8,59) = 5.459$; $p < 0.001$). The MMSE scores of the patients decreased by -0.24 points for each year increase in age and -0.28 points for each point of increase in GDS. On the other hand, the MMSE scores increased by 1 point for 0.49 additional year of education. No significant effect was found with gender, disease duration or drug usage. Having controlled these confounding variables, patients with 25(OH)D levels ≥ 30 ng/ml scored 2.81 points more than the patients with levels < 30 ng/ml. The details of the regression results are shown in Table-2.

DISCUSSION

The results of our study showed that patients with

Table 1. Demographic and disease characteristics of the groups.

	25(OH)D < 30ng/ml (n=51)	25(OH)D ≥ 30ng/ml (n=18)	P value
Age [years], mean (SD)	76.6 (7.8)	75.3 (5.0)	0.46
Male gender [%]	41.2	44.4	0.81
Education [years], mean (SD)	4.9 (4.1)	5.2 (3.6)	0.76
Disease duration [months], mean (SD)	28.8 (28.8)	26.6 (18.6)	0.76
Geriatric Depression Scale, mean (SD)	10.5 (6.5)	8.9 (6.2)	0.40
AChE-inhibitor usage [%]	41.2	44.4	0.81
Memantine usage [%]	20	38.9	0.11
Mini-Mental State Examination , mean (SD)	17.4 (6.0)	20.9 (4.8)	0.027*

SD, Standard deviation; AChE, Acetylcholinesterase * P value < 0.05

AD whose serum 25(OH)D levels lower than 30 ng/ml performed worse in MMSE compared to patients with levels ≥30 ng/ml. Importantly, this result was independent from the confounding effects of age, gender, education, depressive state, disease duration or anti-dementia medication. As expected, we also found a negative relationship of age and depression scores in GDS with the MMSE scores. Likewise, an increase in education level positively correlated with the MMSE scores.

An association between 25(OH)D levels and cognition has been investigated in several cross-sectional studies in adolescents (9), elderly population (10) and individuals diagnosed with cognitive impairment (11). Most of these studies have reported a concordance between 25(OH) D levels and cognitive status. Similarly, the vast majority of the longitudinal studies have also described a close association (12,13), only in contrast to few which have found no such relationship (14). A study conducted in Turkey with 104 neurologically healthy women also reported no association (15). Despite various negative results, the accumulated evidence from the major studies have indicated that 25(OH)D deficiency is an independent risk factor for cognitive decline and dementia (4,13). Nevertheless, interventional studies and randomized-controlled trials with 25(OH)D supplementation have provided limited information due to conflicting results which may be attributed to differences in the recruited population, baseline 25(OH)D levels, supplement doses or follow-up period (16). Even if improvement in cognition was not observed following 25(OH)D supplementation, that may indicate that 25(OH) D, being a risk factor, may play a role in the pathological process, and its augmentation does not alter the neurodegenerative damage which has already occurred.

Our results in AD patients are consistent with those obtained in previous research showing that 25(OH)D is indeed associated with cognitive impairment. In this study, the MMSE scores were also significantly correlated with age, education

Table 2. Regression coefficients of multiple linear regression in the second step.

	B	SE – B	β (95 % CI)	P value
Constant	38.6	7.3	-	-
Age	-0.24	0.09	-0.29 (-0.42 – -0.06)	0.008**
Gender	-0.10	1.6	0.008 (-3.2 – 3.04)	0.95
Education	0.49	0.2	0.33 (0.08 – 0.89)	0.019*
Geriatric Depression Scale	-0.28	0.1	-0.30 (-0.49 – - 0.07)	0.011*
Disease duration	0.003	0.03	0.02 (-0.05 – 0.05)	0.89
AChE-inhibitors	0.006	1.4	0 (-2.9 – 2.9)	1.00
Memantine	-0.89	1.6	-0.07 (-4.1 – 2.3)	0.58
25(OH)D Groups	2.81	1.4	0.21 (0.08 – 5.5)	0.044*

B, Regression coefficient; SE, Standard error; β, Beta value; CI, Confidence interval; AChE. Acetylcholinesterase; 25(OH)D, 25-hydroxyvitamin D
* P value < 0.05, ** P value < 0.01

and depressive state as anticipated. However, no significant association with disease duration was observed (Table-2); this could be related either to the shared variance between disease duration and other included factors or to the information bias generated from determining the disease duration based on symptom onset. Although collected in a uniform fashion, the information was extracted from subjective patient history, which is subjective in nature.

An additional issue that should be taken into account is the inconsistency across studies with regard to the cut-off value for the definition of 25(OH)D deficit. Some studies applied cut-off values at 20 ng/ml (50 nmol/l) and 10 ng/ml (25 nmol/l) to define 25(OH)D insufficiency and deficiency, respectively (12–14). However, ≥ 30ng/ml (≥ 75 nmol/l) was suggested as the adequate level of 25(OH)D by Holick et al., given that the parathyroid hormone levels do not taper down at values lower than 30 ng/ml (8). Therefore, we adapted this cut-off value as the optimal 25(OH)D level and regarded lower values as 25(OH)D insufficiency, which was also recommended by the task force of "Vitamin-D and Cognition in Adults" (17) and used in previous studies (18). Additional analyses with a cut-off value of <10 ng/ml with a definition of 25(OH)D deficiency was not performed due to extreme imbalance between group sizes (data not shown).

The pathophysiological role of 25(OH)D in brain has been demonstrated in several non-human studies. The presence of the 25(OH)D receptor in the brain has been shown, through which 25(OH)D probably exerts its antioxidant effects against glutamate-related mitochondrial neurotoxicity (19). Increase in amyloid clearance has also been detected with overexpression of 25(OH)D receptor (20). Additionally, 25(OH)D is involved in the synthesis of neurotrophic factors such as neurotrophin or nerve growth factor, which mediates growth and reduces the age-related inflammation in the hippocampal region (21). Furthermore, 25(OH)D regulates the expression of neurotransmitters such as acetylcholine, dopamine or serotonin and acts on voltage-gated calcium channels in the brain, thereby modulating calcium-related homeostasis (22). Furthermore, 25(OH)D has been shown to enhance the production of nitric oxide and provide protection against endothelial dysfunction and microvasculopathies (23). The risk for retinopathy, nephropathy and cerebrovascular diseases has been shown to increase in the presence of 25(OH)D deficiency (24), which in turn, is in accordance with the finding that low 25(OH)D levels are associated with not only AD but also vascular dementia (12). These studies elucidate the biological background of the clinical findings that suggest a crucial role of 25(OH)D in the pathophysiological mechanisms leading to a cognitive decline and recommend close monitoring of 25(OH)D levels in elderly individuals (17).

Several limitations of the current study need to be discussed. The effects of age, gender, education, depressive state, disease duration and anti-dementia medication were controlled by including these confounding factors in the regression model; however, additional potential confounders such as calcium and cholesterol levels, kidney functions, body mass index, smoking or alcohol intake, APO-E genotype, as well as socio-economic status, nutrition problems related with disease stage, systemic diseases such as diabetes or heart failure were not assessed in this study. Moreover, cognitive assessment of the patients participating in this study was performed using only MMSE, which does not reveal the details of the cognitive domains. Some previous studies have reported a selective association between 25(OH)D levels and cognitive tasks such as trail making test, digit span, and immediate word recall (25), which could not be tested in this study. Conversion of the MoCA scores into MMSE scores in 11 patients could have also added a bias, although we applied the conversion table designed for patients with

cognitive impairment. The relatively small sample size and the retrospective design are additional shortcomings of the present study.

In conclusion, we showed that patients with AD who had optimal (≥ 30ng/ml) serum 25(OH)D levels exhibited higher MMSE scores than those with inadequate 25(OH)D levels, thereby confirming the association of 25(OH)D concentrations and cognition in Turkish patients with AD. It should also be noted that this association does not imply any causality considering the cross-sectional nature of the study. Given that approximately one third of the elderly population in Turkey has 25(OH) D deficiency (5), the magnitude of the impact of 25(OH)D deficiency on cognition warrants further investigation in Turkish patients with cognitive impairment as well as in healthy elderly adults in future longitudinal studies with larger samples and strict confounder assessments.

CONFLICT OF INTEREST

The authors declare no conflict of interest

FINANCIAL DISCLOSURE

Nothing to report

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