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Original Research / Özgün Araştırma

Vitamin D levels of Alzheimer's patients compared to other neurology clinic applicants. A case-control study

Alzheimer hastalarının D vitamini düzeylerinin diğer nöroloji hastaları ile karşılaştırılması. Bir vaka kontrol çalışması

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ABSTRACT

Introduction: Alzheimer's disease is a progressive neurodegenerative disease that causes cognitive dysfunction. Cognitive impairment may be associated with vitamin D deficiency. This study aims to determine vitamin D levels and frequency of deficiency in Alzheimer's patients and to compare it with other patients of similar age group applied to the neurology clinic.

Methods: The hospital records of patients who were seen in the neurology clinic between 01/01/2018 and 31/12/2020 and of whom 25 (OH) Vitamin D3 levels were measured were included. In addition to Alzheimer's patients, the control group was randomly selected from the records of patients with no cognitive disorder with similar age and gender.

Results: Of patients, 156 records were included in the Alzheimer group and 442 in the control group. There were 95 women (60.9%) 61 men (39.1%) in the Alzheimer group, 271 women (61.3%) 171 men (38.7%) in the control group. There was no significant difference between the mean age of the Alzheimer group (75.9) and control group (75.4). No significant difference was detected between the mean vitamin D levels of Alzheimer's patients (21.5±12.4 ng/ml) and control group (20.1±13.1 ng/ml). There was no significant difference between the genders. Vitamin D levels of "85 years and above" were significantly lower than those of the "75-79 years old", "70-74 years" and "65-69 years old" groups.

Conclusion: The mechanisms of vitamin D on the pathophysiologic pathways of Alzheimer disease have not been fully elucidated. According to our results, vitamin D levels are not significantly different between Alzheimer's patients and controls. Low vitamin D may be an effective factor in the development of Alzheimer's disease, but after the disease occurs, vitamin D levels do not differ from other patients of similar age and gender.

Key words: 25(OH) Vitamin D, Alzheimer Disease, Cognition

ÖZET

Amaç: Alzheimer hastalığı, kognitif fonksiyon bozukluğu yapan ilerleyici nörodejeneratif bir hastalıktır ve hastalığın göstergesi olan kognitif bozulmanın yaşlanma ile belirgin hale gelen D vitamini eksikliği ile ilişkili olabileceği ile ilgili çalışmalar yapılmıştır. Bu çalışmada Alzheimer hastalarında D vitamini düzeylerini belirlemek, eksiklik durum sıklığını saptamak ve benzer yaş grubu hastalarla karşılaştırmak amaçlanmıştır. **Yöntem:** Bu çalışmaya 01/01/2018 ve 31/12/2020 tarihleri arasında Nöroloji kliniğinde görülen ve 25(OH) Vitamin D3 düzeyleri ölçülmüş hasta kayıtları dahil edilmiştir. Alzheimer hastalarına ek olarak kontrol grubu, nöroloji polikliniğinde görülen, kognisyon bozukluğu olmayan hastalara ait kayıtlardan yaş ve cinsiyet olarak benzer özellikte, rastgele seçilmiştir. **Bulgular:** Çalışmaya 156 Alzheimer ve 442 kontrol grubunda hasta kayıt dahil edildi. Alzheimer grubunda 95 kadın (%60,9), 61 erkek (%39,1) kontrol grubunda 271 kadın (%61,3), 171 erkek (%38,7) bulunmaktaydı. Alzheimer grubu yaş ortalaması (75,9) ile kontrol grubu yaş ortalaması (75,4) arasında anlamlı fark yoktu. Vitamin D düzeyi ortalama değeri Alzheimer hastalarında 21,5±12,4 ng/ml ve kontrol grubunda 20,1±13,1 ng/ml olup anlamlı fark yoktu. Cinsiyetler arasında anlamlı fark yoktu. 85 yaş ve üzeri" Vitamin D düzeyleri "75-79 yaş", "70-74 yaş" ve "65-69 yaş" gruplarından anlamlı düşüktü. **Sonuç:** D vitaminin AH üzerindeki etki mekanizmaları tam olarak açıklığa kavuşturulamamıştır. Çalışma sonuçlarımıza göre Alzheimer hastaları ile kontroller arasında D vitamin düzeyleri anlamlı farklı değildir. D vitamini düşüklüğü Alzheimer hastalık gelişiminde etkili bir etmen olabilir ancak hastalık ortaya çıktıktan sonra D vitamini düzeyleri benzer yaş ve cinsiyette diğer hastalardan farklılık göstermemektedir.

Anahtar Kelimeler: 25(OH) Vitamin D, Alzheimer Hastalığı, Kognisyon

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1.INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease that causes cognitive dysfunction. The incidence and prevalence of Alzheimer's disease are increasing strikingly every year. The prevalence of AD in individuals over the age of 70 is reported as 11%.[1] Vitamin D has a neuroprotective effect in the elimination of amyloid plaques formed in the brain in AD.[2] With the increase in age and the decrease in plasma vitamin D amount, cognitive function is found to be more impaired compared to people with normal vitamin D levels.[3] It has also been reported that cognitive functions improved in AD with vitamin D treatment.[4,5] In some studies, differently, it was stated that the relationship between cognitive functions and vitamin D level is not fully clear.[6]

Alzheimer's disease has a multifactorial etiology. Vitamin D function in the etiopathogenesis of AD is still not fully clear. The inconsistency in the studies may be since inclusion criteria, statistical analysis, and confounding factors such as vitamin D use were not evaluated clearly.
The aim of this study is to evaluate the vitamin D levels and the prevalence of vitamin D deficiency in AD patients and to compare them with controls.

2.METHODS

The study was conducted on the health records in the registration system of Çanakkale Onsekiz Mart University Hospital. For the study Çanakkale Onsekiz Mart University Clinical Research Ethics Committee approval was obtained. The study was designed in a case-control design, and study and control groups were formed. The data of patients who were seen in the Neurology Clinic of the University Hospital between 01/01/2018 and 31/12/2020 and whose 25 (OH) Vitamin D3 levels were measured formed the selection universe. Those with incomplete or inconsistent information, duplicate records were excluded. To avoid the effect of increases due to vitamin D use, those with more than one vitamin D measurement were based on the oldest measurements. Under 55 years of age were excluded from the study population.

From the selection universe, those who had a diagnosis of AD (ICD codes of G30.0-Alzheimer's disease, early-onset, G30.1-Alzheimer's disease, late-onset, G30.8-Alzheimer's disease, other, G30.9-Alzheimer's disease, F00-Dementia, Alzheimer's disease, F00.9- dementia in Alzheimer's disease, undefined, unspecified) formed the study group. All 156 records meeting these conditions were included in the study group.
For the control group selection, excluding those with vitamin D deficiency and other diseases that impair cognition (ICD codes of F01, F02.8, F02, F05.1, F05.8, F05.9, F06, F06.7, F32-, F32.8, F32.9 F99, G10, G20, G30, G35, D51, D51.8, E03.9, E55), the remaining 1151 records were used. The records were stratified in terms of gender and age (divided into age groups 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, and> 85). According to random numbers assigned for every record, the control group was formed containing the number of AD records for each stratum. All records were included in the stratum with less than the specified number of records for the control group. The control group consisted of a total of 442 records. Included counts of records according to the strata in the AD and control groups are given in Table 1.

Table 1. Patient record counts included in study groups by gender and age ranges

	Alzheimer group		**Control group**	
	Female n (%)	**Male** n (%)	**Female** n (%)	**Male** n (%)
55-59 years	3 (3.2)	1 (1.6)	9 (3.3)	3 (1.8)
60-64 years	3 (3.2)	1 (1.6)	9 (3.3)	3 (1.8)
65-69 years	11 (11.6)	11 (18.0)	33 (12.2)	33 (19.3)
70-74 years	19 (20.0)	14 (23.0)	57 (21.0)	52 (30.4)
75-79 years	31 (32.6)	13 (21.3)	88 (32.5)	39 (22.8)
80-84 years	17 (17.9)	10 (16.4)	42 (15.5)	30 (17.5)
85 years and over	11 (11.6)	11 (18.0)	33 (12.2)	21 (12.3)
TOTAL	95 (100.0)	61 (100.0)	271 (100.0)	171 (100.0)

In our hospital's biochemistry laboratory, plasma 25 (OH) Vitamin D measurements are measured by chemiluminescent immunoassay and colorimetric assay techniques.

Statistical analysis

The dependent variable of the study was Vitamin D level, and the independent variables were age and gender variables. Vitamin D levels were classified as adequate (>30 ng/ml), insufficiency (<30-≥20 ng/ml) and deficiency (<20 ng/ml). Vitamin D level and classification were analyzed whether there was any difference between the study and control groups and in terms of independent variables.

After the study data was analyzed, frequency and percentage values for categorical variables, mean and standard deviation values for continuous variables were reported. Analyzes were performed using the Chi-square test, Student t-test, Pearson correlation test,and Kruskal-Wallis test in

accordance with variable characteristics. Since the sample size number is larger than 30, the normal distribution assumption has been neglected in parametric tests based on the central limit theorem. The general significance limit for all analyzes was accepted as $p<0.05$, and test constants and absolute p values were given for each analysis.

3. RESULTS

The study group consisted of 156 and the control group consisted of 442 records. There were 95 women (60.9%) 61 men (39.1%) in the AD group, 271 women (61.3%), 171 men (38.7%) in the control group, there was no significant difference between the groups (X^2=0.008; p=0.927). There was no significant difference between the mean ages of the AD group (75.9 years) and the control group (75.4 years) (t=0.676; p=0.499). There was no significant difference between the study and control groups in terms of age groups (X^2=0.560; p=0.996).

The mean Vitamin D level was 21.5 ± 12.4 ng/ml in the AD group, and 20.1 ± 13.1 ng/ml, in the control group and there was no significant difference between the groups (t=1.134; p=0.257).There was no significant difference between the genders in terms of the mean vitamin D levels in the AD group (t=1.020; p=0.309) or the control group (t=1.554; p=0.121).

Vitamin D level showed a significant negative correlation with age (r=-0.128; p=0.002). While this trend was present in the control group (r=-0.169; p<0.001), it was not present in the AD group (r=-0.010; p=0.899). The change of vitamin D levels in age groups in the AD and control groups is shown in Figure 1. There was no difference in vitamin D levels between age groups in the study group (Kruskal-Wallis X^2=6.257; p=0.395). A significant difference was detected in vitamin D levels between age groups in the control group (Kruskal-Wallis X^2=33.372; p<0.001). Post hoc analysis revealed that vitamin D levels in the age group of "85 years and over" were significantly lower than the "75-79 years", "70-74 years" and "65-69 years" age groups.

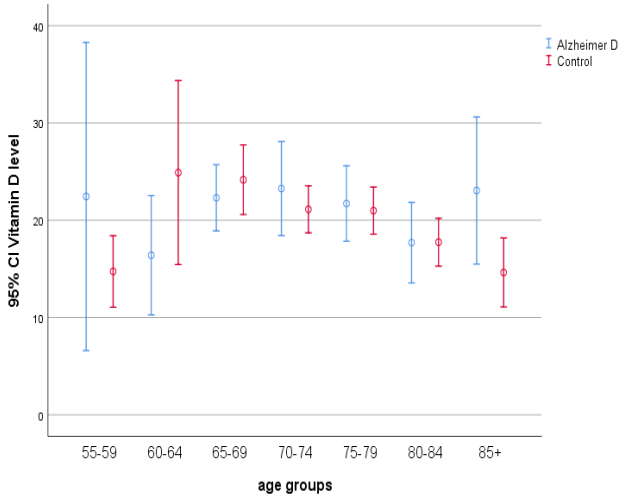

Figure 1. Vitamin D levels by age ranges

There was a significant difference between the AD and control groups in terms of vitamin D level groups (X^2=9.872; p=0.007) (Table 2). While the deficiency of vitamin D in the AD group was significantly lower than the control group, the insufficiency of vitamin D was significantly higher, the rates of adequate levels of vitamin D were not different between the two groups.

Table 2. Vitamin D levels in the study groups

Vitamin D level	Alzheimer group n (%)	Control group n (%)	Total n (%)
Deficiency (<20 ng/ml)	76 (49.0)[a]	273 (61.8)[b]	349 (58.5)
Insufficiency (<30 - ≥20 ng/ml)	50 (32.3)[a]	91 (20.6)[b]	141 (23.6)
Adequate (>30 ng/ml)	29 (18.7)[a]	78 (17.6)[a]	107 (17.9)

[a] [b] Each letter represents a different subcategory for column ratios, the significance level was taken as 0.05, Bonferroni correction for multiple analyses was applied.

3.DISCUSSION

AD, which is one of the most common neurodegenerative diseases that occur with damage and loss of neuron cells, is an irreversible, progressive disease responsible for the majority of dementia patients.[7] Alzheimer's disease accounts for 60-70% of dementia cases. In the 2015 World Alzheimer's Report, it was determined that 46.8 million people worldwide live with dementia and the total social cost of dementia was found to be approximately 818 billion USD.[8]

It has been shown that inflammation in the brains of AD patients is persistent. Aβ (amyloid-beta) itself is a pro-inflammatory agent. When Aβ or other toxic products accumulate in excess, pro-inflammatory reactions are activated, damaging neurons.[9] The accumulation of Aβ fibrils in the

brains of Alzheimer's patients begins decades before clinical symptoms show.[10]

Since vitamin D deficiency increases in the elderly population, it is thought that there may be a relationship between cognitive damage, AD, and D hypovitaminosis with aging. Many studies have been conducted showing the positive effects of vitamin D on pathological findings and cognitive damage in AD, and some studies have shown that the use of vitamin D has a therapeutic effect.[11,12]

Vitamin D has antioxidant properties and has a neuroprotective effect. In the study conducted on rats, 1,25 $(OH)_2$ vitamin D3 has been shown to increase myelinization in the hippocampus region of the brain, and vitamin D reduces demyelination by showing anti-apoptotic properties.[13] It is known that free Ca^{+2} has a neurotoxic effect on the central nervous system. Vitamin D prevents the formation of calcium chelates within the cell by stimulating the expression of calcium binding proteins. However, in a study conducted on rats, the effect seen in the kidney was not seen in the brain.[14]

In experimental studies, it has been suggested that low vitamin D may mediate neurodegenerative processes related to AD.[15] Case-control studies in humans have shown that individuals with dementia or AD have lower circulating concentrations of 25 (OH) vitamin D. Also, several longitudinal studies have found an association between lower baseline 25 (OH) vitamin D concentrations and rapid cognitive decline, although conflicting results have persisted.[16]

In a review covering studies from 1979 to 2008 and in which five of the 99 selected studies met the selection criteria and were included in the final analysis, it was shown that the relationship between serum 25 (OH) vitamin D concentrations and cognitive performance was not established. The results of the studies reviewed may result from the methodology of measuring vitamin D levels, the types of cognitive tasks used, and/or cellular mechanisms.[8]

In a study with 40 mild AD and 40 unidentified total 80 participants, there was no difference in cognitive function between the vitamin D groups.[17] In the population-based NHANES III screening, in the adolescent and adult groups, none of the psychometric measures correlated with 25 (OH) vitamin D levels. There was a significant difference between 25 (OH) vitamin D levels and performance in learning and memory tasks in the elderly group; however, those with the highest quartile of 25 (OH) vitamin D showed the highest degradation in tasks, contrary to assumptions.[18]

No association was found out between baseline vitamin D status and the risk of dementia or AD in the Framingham Heart Study.[19] The US study of 1658 elderly community residents found an increased risk of AD and all-cause dementia among participants with 25 (OH) vitamin D insufficiency/deficiency.[20] Seasonally adjusted reduction in plasma 25 (OH) vitamin D levels have been associated with an increased risk of AD in the Danish National Patient Registry.[21] In a large prospective cohort study for dementia, after 12 years of follow-up, vitamin D deficiency (<25 nmol/L) was associated with faster cognitive decline and an approximately three-fold increased risk of AD. The association between vitamin D and AD seemed particularly strong. The findings were interpreted as that keeping plasma 25 (OH) vitamin D concentrations of 50 nmol/L or above in elderly people may contribute to the preservation of brain health and a lower risk of AD.[22]

In the literature, reports on 25 (OH) vitamin D status and cognitive decline are mixed and appear to depend on several factors such as gender, age, and cognitive domains evaluated. Our study was conducted retrospectively and factors known to affect circulating 25 (OH) vitamin D concentration, such as genetic variants of the VDR gene, were not included in the evaluation. Although the use of vitamin D supplements was tried to be excluded as much as possible, full control could not be achieved on this issue.

The results of studies investigating the effect of vitamin D level on cognitive functions in AD show differences. According to our study results, vitamin D levels are not significantly different between AD patients and controls. Low levels of vitamin D may be an effective factor in the development of AD, but after the disease settled, vitamin D levels do not differ from other patients of similar age and gender. Since the mechanism of action of vitamin D in AD is not fully clear, controlled studies are needed.

According to the results of the study, Vitamin D insufficiency is more, and deficiency is less common in Alzheimer's patients compared to controls while there was no difference in those with sufficient Vitamin D levels. Since there was no significant difference between the groups in terms of absolute vitamin D levels, this was interpreted as relatively less important. Regular control of vitamin D levels in Alzheimer's patients may have a preventive effect on deficiency in patients. The observed relationships between age and vitamin D

levels are not decisive and may be influenced by patient selection characteristics.

Since this is a cross-sectional study, results do not give clues about what kind of changes will occur in the vitamin D levels of a single patient during the aging and disease processes over time. In addition, the control group consisted of only patients admitted to the hospital and did not reflect the whole society. The results should be interpreted appropriately and carefully.

Conclusion

AD is a progressive neurodegenerative disease and the role of vitamin D in disease processes has not been fully elucidated. According to our study results, vitamin D levels in AD patients were not significantly different from other patients of similar age and gender. Although many studies are investigating the relationship between vitamin D and AD, the results still contain contradictions. Studies on the effect of vitamin D on AD are still needed.

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