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Original Article

Assessment of Serum 25-hydroxyvitamin D Levels at the First Manifestation of Multiple Sclerosis in Children and Adolescents

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ABSTRACT

Objective: To evaluate serum 25-hydroxyvitamin D levels, demographic features, and anthropometric measurements at the first manifestation of disease in children and adolescents with multiple sclerosis (MS).

Methods: This retrospective study included patients with MS and healthy children and adolescents. Children and adolescents whose clinical and radiological findings were compatible with the McDonald 2017 criteria and who had vitamin D results during the first relapse were included. Having an acute or chronic disease was an exclusion criterion for healthy controls. Taking a supplementation including vitamin D is an exclusion criterion for both the MS and control groups. Age, gender, anthropometric measurements, and serum levels of 25-hydroxyvitamin D were extracted from the database.

Results: A total of 23 patients (female: 17, 73.9%) and 24 (female: 12, 50.0%) healthy children and adolescents were included. The median ages of the patient group and the control group were 16.33 (2.00), and 15.36 (2.29), respectively. There were no significant differences between the groups in terms of age, gender, weight-standard deviation score (SDS), height-SDS, and body mass index-SDS. Precisely, 87.0% of the patients had a vitamin D deficiency. The mean vitamin D values of the patients and the healthy controls were 12.76±5.52, and 18.75±5.86, respectively. Patients with MS had significantly lower levels of 25-hydroxyvitamin D than healthy controls ($p<0.0001$).

Conclusion: The current study showed that most (87.0%) of the children and adolescents had vitamin D deficiency at the first manifestation of MS. Moreover, the levels of 25-hydroxyvitamin D levels were significantly lower in patients with MS than in the healthy controls.

Keywords: Multiple sclerosis, vitamin D, 25-hydroxyvitamin D, children, adolescents, the first manifestation, height

INTRODUCTION

Vitamin D is a lipid-soluble vitamin. Calcitriol is the active form of vitamin D and has a chemical resemblance to steroidal hormones. Exposure to sunlight, diet, and taking supplements including vitamin D are the main resources.[1,2] The richest source is exposure to sunlight, especially during the summer months. However, there may be a reduction in the synthesis of vitamin D in people who have dark skin, with an older age, and people who use sunscreen. Moreover, environmental factors including the winter, high latitude, pollution, cloudy weather, and ozone levels have also have negative effects on the synthesis of vitamin D.[3]

The relationship between bone health and vitamin D deficiency has been known since the early 1900s. However, studies have shown that low levels of vitamin D have been related to various diseases such as cancers, cardiovascular diseases, type 2 diabetes mellitus, Chron's disease, and multiple sclerosis (MS).[4] In the 1970s, it was suggested that vitamin D played a role in the development and progression of MS. MS is the most prevalent-demyelinating

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disease that affects myelin that covers the nerve cells in the brain and spinal cord.[5] The disease has negative impacts on physical, mental, and psychiatric well-being. It can be considered a relapsing-remitting form when new symptoms occur during the attacks and a progressive form when new symptoms build-up without an attack.[6] Relapsing-remitting is more common in children and adolescents. Though the exact pathophysiological mechanism is not well understood, both genetic and environmental factors have roles in pathogenesis. Obesity, Ebstein-Barr virus infection, vitamin D deficiency, and smoking are proposed as environmental risk factors.[7-10] Sufficient levels of vitamin D are one of the protective factors for MS, which could have roles at different times between conception and the disease manifestation. Some epidemiological research showed that the prevalence of MS is higher in regions with lower exposure to sunlight. However, some genetic errors in the vitamin D metabolism indicate an association with MS and it was suggested that ultraviolet B (UVB) had not a beneficial role in the immunity.[11] The Endocrine Society suggests that a lower level of 25-hydroxyvitamin [25(OH)D] than 20 ng/mL is a deficiency, a level between ≥20 ng/mL and <30 ng/mL is insufficiency, and a level higher than 30 ng/mL is sufficiency.[12] There are also studies suggesting that in the presence of adequate levels of vitamin D, the risk and activity of the disease decrease.[13,14] Furthermore, it was proposed that lower levels of vitamin D in the first part of life are related to a major risk of MS.[15]

Here, we investigated the demographic features, anthropometric measurements, levels of 25(OH)D, and the ratio of insufficiency and deficiency of vitamin D in children and adolescents with MS at the first manifestation of the disease.

MATERIALS AND METHODS

The approval of the ethics committee has been obtained from Aydın Adnan Menderes University Non-Invasive Clinical Research Ethics Committee in line with the principles outlined in the Second Declaration of Helsinki (approval number: 2022/90). Informed consent was not required because of the retrospective design. This retrospective case-control study was conducted from January 2006 to April 2022 at Aydın Adnan Menderes University Faculty of Medicine, Department of Pediatric Neurology. The inclusion criteria were as follows; i) children and adolescents whose clinical and radiological findings were compatible with McDonald 2017 criteria, ii) patients with MS who had vitamin D results during the first relapse. The control group consisted of healthy children who were admitted to the General Pediatrics Outpatient Clinic for examination and had vitamin D results during the admission. Having an acute or chronic disease was an exclusion criterion for the control group. Additionally, taking a supplement including vitamin D was an exclusion criterion for both the patient and control groups. The diagnosis of MS was made by two pediatric neurologists. Demographic features including age, gender, weight-standard deviation score (SDS), height-SDS, body mass index (BMI)-SDS, and the levels 25(OH)D were extracted from the electronic database.

Statistical Analysis

Statistical analyses were performed using the SPSS-22 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). The Shapiro Wilk test was applied to specify the normal distribution of numerical variables. Categorical data were presented as n and %. Normally distributed numerical data were presented with mean ± SD, and non-normally distributed data presented with median (interquartile range). Student t-test was applied for the comparison of normally distributed data, and the Mann-Whitney U test was used for the comparison of non-normally distributed data. The chi-square test was used for the comparison of categorical data. A p-value <0.05 was set as statistically significant.

Table 1. Comparison of the demographical features and levels of 25-hydroxyvitamin D between patients with multiple sclerosis and healthy controls

	Multiple sclerosis (n=23)	Control (n=24)	p-value
Age**	16.33 (2.00)	15.36 (2.29)	0.124
Gender			
• Female	17 (73.9%)	12 (50.0%)	0.092
• Male	6 (26.1%)	12 (50.0%)	
Weight-SDS**	0.82 (2.98)	0.03 (3.01)	0.160
Height-SDS**	0.39 (1.69)	0.040 (1.38)	0.758
BMI-SDS*	0.56 ± 1.56	-0.24±1.81	0.109
Levels of 25-hydroxyvitamin D categorization**			
- Sufficiency (≥30 ng/mL)	0 (0%)	0 (0%)	**0.028**
- Vitamin D insufficiency (between ≤20 ng/mL and <30 ng/mL)	3 (13.0)	10 (41.7%)	
- Vitamin D deficiency (<20 ng/mL)	20 (87.0%)	14 (58.3%)	
Levels of 25-hydroxyvitamin D* (ng/mL)	12.76±5.52	18.75±5.86	**<0.0001**

*Non-normally distributed data were given as median (IQR).

**Normally distributed data were given as mean (± SD).

IQR: Interquartile range, SD: Standard deviation, SDS: Standard deviation score, BMI: Body mass index

RESULTS

The study group consisted of 23 patients (17 female, 6 male) and 24 healthy children and adolescents (12 female, 12 male). All the patients had a relapsing-remitting form of MS. The median age of the patient group and the control group were 16.33 (2.00), and 15.36 (2.29), respectively. There were no significant differences between the groups in terms of age, gender, weight-SDS, height-SDS, and BMI-SDS. Of the patients, 87.0% had a vitamin D deficiency. Neither the patients nor the healthy controls had a sufficient vitamin D level. The mean vitamin D values of the patient group and the control group were 12.76±5.52 ng/mL, and 18.75±5.86 ng/mL, respectively. The serum levels of 25(OH)D were significantly lower in the patient group than in those healthy controls during the first relapse ($p<0.0001$) (Table 1).

DISCUSSION

The major findings of the current study were as follows; i) most of the patients (87.0%) had a vitamin D deficiency, and ii) serum 25(OH)D levels during the first attack were significantly lower in patients with MS than in those healthy controls.

The frequency of MS decreases around the equator and increases around the North and South latitudes.[16] Moreover, immigration from North and South latitudes to the equator during the first two decades may decrease the prevalence.[17] Also, a longer duration of time spent outdoors decreases the risk of MS in later life.[18] In a meta-analysis of 52 studies by Sloka et al.[19], it was found that MS prevalence was 20 times higher in the countries where the annual amount of UVB is the lowest. This study was conducted at Aydın Adnan Menderes University, located in Aydın province, in the Aegean Region of Turkey (latitude: 37° 50' 42.04'' N, longitude: 27° 50' 22.67'' E). Since the hospital is a 3rd-level center we had the opportunity to examine and follow children and adolescents from the province, and neighboring provinces. Although the climate of the Aegean Region is scalding in the summer, none of the children and adolescents had a sufficient serum level of 25(OH)D in the current study. Also, most of the patients (87.0%) with MS had a vitamin D deficiency at the first manifestation of the disease. Similarly, a high rate of insufficient levels of vitamin D was found in children and adolescents, in a study, which was conducted in the Aegean Region.[20] In another study, it was found that 74.9% of 209 adults had lower levels of 25(OH)D than 20 ng/mL.[21] Thus, despite the hot climate, especially in the summer, vitamin D deficiency may be a common problem in Agean Region. The cause of the results may be related to decreased exposure to sunlight, such as using sunscreen, wearing clothes that restrict exposure to sunlight, and/or an increased tendency to spend time indoors.

Lower levels of vitamin D than 20 ng/mL have been found in some studies before the first manifestation of MS.[22-24] However, since the disease is multifactorial, sufficient levels may be seen in patients. Behrens et al.[22] conducted a study to assessed serum levels of 25(OH)D in 76 adult patients with MS at the first manifestation of the disease and 76 healthy controls. It was found that patients with MS have significantly lower levels of 25(OH)D than the healthy controls. Martinelli et al.[23] demonstrated that low baseline levels of 25(OH)D were a risk factor for MS in patients with the clinically isolated syndrome. Moreover, the odds ratios were 3.34 [confidence interval (CI) 95%: 1.32-8.75], and 2.04 (0.9-4.36) for lower levels than the 10th percentile, and 25th percentile, respectively.[23] Munger et al.[24] performed a study among USA soldiers whose blood samples were stored. The levels of 25(OH) D, which were stored before the initial symptoms of the disease, were analyzed and compared with the age-matched healthy controls. Among whites, levels of 25(OH)D were significantly lower in patients with MS (n=148) than in the healthy controls (n=296). However, an association could not be found between the levels of 25(OH)D and MS risk among blacks and Hispanics (n=109 patients, n=218).[24] Additionally, a lower MS risk was found in people who were born in fall than in those who were born in spring. It was proposed that the results may be associated with the levels of 25(OH)D during the pregnancy since lower levels, and higher levels exist in babies who were born in spring, and autumn, respectively.[25] In this study, serum levels of 25(OH)D were significantly lower in patients with MS than in those healthy controls.

The relationship between vitamin D and MS has been explained by the immunomodulatory role of vitamin D.[26] There is research showing multiple immunological favorable effects obtained after vitamin D supplementation in patients with MS. The beneficial effects consisted of stimulation of Tregs, attenuation of B-cell autoimmune reactivity, and favorable changes in cytokines.[27,28] In addition to the immunomodulatory effects, vitamin D has neuroprotective, neurotrophic, and remyelinating effects by entering the cells in the central nervous system.[29] There are studies demonstrating the association between MS risk and various genetic abnormalities of the histocompatibility complex of the human leukocyte antigens, and gene variants concerning the metabolism of vitamin D. Also, a linkage between genetically low vitamin D levels and MS risk has been found recently.[9]

Several studies exist regarding the relationship between obesity and MS. In a study by Munger et al.[30] which was conducted on women, BMI ≥30 kg/m^2 at the age of 18 is a risk factor for developing MS after adjusting for the other risk factors (odds ratio: 2.25, 95% CI: 1.50-3.37). In a study from Norway and Italy, it has also been demonstrated the risk of MS 2-fold increases in the presence of obesity.[31] Also, in two studies, it has been suggested that obesity is a risk factor for MS or clinically isolated syndrome in pediatric patients.[32,33] In a prospective study among 302043 children between the ages 7-13, it was proposed that having a higher BMI in childhood was a risk factor for developing MS.[32] This causal relationship has been explained recently. It was suggested that some gene variants for obesity result in MS susceptibility. Additionally, it was proposed that socioeconomic status had similar impacts on both MS and obesity.[34,35] There is research regarding the relationship between obesity, final height, and vitamin D status. There was a negative correlation between obesity and vitamin D levels. It was suggested that α-1hydroxylase

has a negative impact on adipogenesis.[36] Also, it was shown that obese people have relatively lower levels of vitamin D than the non-obese controls even after the supplementation with vitamin D.[37,38] The probable cause was explained by the fact that in the presence of increased body fat, vitamin D was trapped in the fat tissue and resulted in low levels of circulating vitamin D.[39] In this study, there were no significant differences between patients with MS and healthy controls in terms of weight-SDS, height-SDS, and BMI-SDS. The absence of an association may be due to the smaller sample size in this study.

Study Limitations

There were some limitations to the current study. First, the retrospective design may lead to the risk of bias. Second, the study was performed in a single center with a small sample size. However, the current study is one of the few studies assessing the levels of serum 25(OH)D at the first disease manifestation in children and adolescents with MS. Also, being a 3rd-level center in the region allowed us to follow patients in Aydın province and from neighboring provinces. Research is needed with a larger sample size of patients with MS and healthy children and adolescents assessing serial analysis of serum 25(OH)D levels and anthropometric measurements.

CONCLUSION

In conclusion, our study shows that the levels of 25(OH)D are significantly lower in patients with MS than in the healthy controls at the first attack of the disease. Additionally, despite the hot climate, vitamin D deficiency may be a common disorder in the region, even in the healthy controls.

Ethics

Ethics Committee Approval: The approval of the ethics committee has been obtained from Aydın Adnan Menderes University Non-Invasive Clinical Research Ethics Committee in line with the principles outlined in the Second Declaration of Helsinki (approval number: 2022/90).

Informed Consent: Informed consent was not required because of the retrospective design.

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Authorship Contributions

Concept: M.A., A.T., Design: M.A., A.T., Data Collection or Processing: M.A., A.T., Analysis or Interpretation: M.A., Literature Search: M.A., Writing: M.A.

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