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Serum 25-Hydroxyvitamin D level in Restless Legs Syndrome: A controlled study

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ABSTRACT

Objective: We aimed to investigate 25-hydroxyvitamin D (25-OHD) level on a group of restless legs syndrome (RLS) patients.

Material and Methods: Twenty-one RLS patients and fourteen age and gender healthy controls (non RLS) with similar age and gender were included in the study. All patients underwent a physical examination for the neurologic and musculoskeletal system. The 25-OHD level was measured for all participants.

Results: The 25-hydroxyvitamin D levels were higher in the RLS patient group (20.06±8.79 ng/ml) than in the healthy control group (14.75±4.67 ng/ml). In the healthy control group ‘’without the RLS syndrome’’, 25-hydroxyvitamin D levels were below the normal range (<20 ng/ml). However, there were no statistical differences in terms of vitamin D level between the RLS and Control groups (p>0.05).

Conclusion: In this study, due to the absence of RLS syndrome in the control group despite low 25-hydroxyvitamin D levels (<20 ng/ml), a relationship could not be established between 25-hydroxyvitamin D levels and RLS syndrome. The cause of RLS syndrome does not seem to depend on a single parameter such as 25-OHD level.

Keywords: Movement Disorder; Restless Legs Syndrome; 25-hydroxyvitamin D

INTRODUCTION

Restless legs syndrome (RLS) is also known as Willis-Ekbom disease (WED) and a neurological movement disorder characterized by the urge to move legs due to uncomfortable and unpleasant sensations in the legs (1). The RLS syndrome was first described by Thomas Willis in 1685. It is Ekbom, which in 1945 defined all the clinical features of the syndrome and named "restless leg syndrome"(2). Because of the cognitions of these pioneers, the nonprofit Restless Legs Syndrome Foundation’s name was changed as the Willis -Ekbom Disease Foundation (3). The diagnosis RLS based on 2012 revised International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria. All the essential criterias for RLS are: 1- The urge to move legs due to feelings of uncomfortable and unpleasant sensation 2- The urge to move legs and feelings of uncomfortable and unpleasant sensation begin or worsen during periods of rest or inactivity such as lying down or sitting 3- The urge to move the legs and unpleasant sensations partially or totally relieved by movement such as walking or stretching 4- The urge to move and unpleasant sensations that occur during rest or inaction; occurs only in the evening or at night or gets worse at this time 5- The above features are not caused by other medical or behavioural conditions such as arthritis, leg cramps, myalgia, venous stasis, leg oedema. (4). Primary RLS is associated with genetic factors that disrupt the brain's iron metabolism, dopaminergic system dysfunction (5). In some studies, it has been reported that vitamin D is the protector of dopaminergic neurons in the nigrostriatal region. Also, vitamin D deficiency is associated with neuropsychiatric diseases such as dementia, multiple sclerosis (MS), parkinsonism (6,7).

There are few studies reporting the relationship between vitamin D and RLS. In this study, we aimed to investigate the 25-hydroxyvitamin D (25-OHD) level of RLS patients and paired control group to evaluate the relationship between 25-OHD level and RLS.

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MATERIAL and METHODS

The study protocol was approved by the Institutional Review Board of the Başkent University ethics committee (protocol number: KA12/222, date: 12/12/2012). The Declaration of Helsinki protocols were followed. All participants were informed about the study and signed written informed consent before interventions.

Twenty-one RLS patients and fourteen healthy volunteers were included to study. Age and gender healthy controls with similar age and gender were selected. Determination of RLS was based on the 2012 revised International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria (8, 9). All RLS patients did not receive any medical treatment related to this diagnosis.

Patients with severe liver and kidney failure, severe neurologic disorder, polyneuropathy, diabetes mellitus, vitamin B12 deficiency, iron and ferritin deficiency, uncontrolled hypo/hyperthyroidism were excluded. The age distribution of all participants was in the range of 18-70. All patients were examined for any musculoskeletal or other disease that can cause pain. All patients underwent a physical examination for musculoskeletal and neurological systems.

Serum 25-OHD levels of all participants were measured using Shimadzu Prominence high performance liquid chromatography (HPLC) (Shimadzu Scientific Instruments, Kyoto, Japan). According to the recommendations of the US Endocrine Society; 25-OHD <20 ng/ml (50 nmol/l) levels vitamin D deficiency; values between 21 and 29 ng / ml (between 52.5 and 72.5 nmol) were defined as vitamin D insufficiency and 25-OHD level> 30 ng/ml (75 nmol/l) as the optimal level (10).

The means and standard deviations were given as descriptive statistics. All data for normality was tested by using Kolmogorov-Smirnov test. To compare the differences between two groups, Mann Whitney U was used. A level of significance of $p<0.05$ was accepted. All analyses were performed using the SPSS for Windows 18.0 software program.

RESULTS

Of the 35 participants included in the study, Group 1 (n = 21) constituted the RLS group, while Group 2 (n = 14) was the healthy control group (non RLS group). The demographic characteristics and 25-OHD levels of the patients and healthy controls are presented in **Table 1**.

While there was a statistically significant difference between the groups in terms of age ($p <0.05$), there was no difference in gender ($p> 0.05$). 25-OHD levels were higher in the RLS group than in the control group. There was no difference in 25-OHD levels between the groups ($p> 0.05$) (**Table 1**).

DISCUSSION

In our study high 25-OHD level was found in RLS patients but there were no significant differences between groups. Restless legs syndrome (RLS), is a common neurological, sensorimotor disorder manifested by an urge or a need to move the limbs to stop unpleasant sensations in the evening or while at rest (1, 11-14). Most of RLS cases appear by idiopathic origin (5). The pathophysiology of RLS is not known precisely but genetic factors, iron deficiency and the dopaminergic system may be a role in RLS. Genetic factor is also important for the pathophysiology of RLS. In a study, it was reported that 63% of patients had first degree kinship (15). Secondary RLS may be caused by underlying medical conditions such as iron deficiency anaemia, renal failure, and pregnancy (5).

In some studies, it is stated that iron deficiency or irregularity is the most important mechanism for understanding the pathophysiology of RLS. Circadian changes in brain iron status appear to be important for RLS (16). Tyrosine hydroxylase is an important enzyme for dopamine synthesis and it uses iron as a cofactor. Therefore, RLS becomes a sensorimotor dysfunction (12-14).

Vitamin D is a fat-soluble prohormone nutrient that has skeletal and extra-skeletal functions. In some studies, lower vitamin D status was found in association with neuropsychiatric diseases such as dementia, MS, bipolar disorders (6, 7). Also, vitamin D has an essential function for the dopaminergic system; it regulates nervous system function (17). In human and rat substantia nigra, tyrosine hydroxylase positive neurons have a vitamin D receptor in the nucleus (18).

It has been reported that 1-alpha, 25- (OH) (2) D (3) reduces oxidative stress and therefore plays a role in protecting dopaminergic neurons against cytotoxicity caused by glutamate and dopaminergic toxins (19).

RLS relation with the dopaminergic system; and due to the relationship between dopaminergic neurons and vitamin D, we investigated 25-OHD in a group of restless leg syndrome (RLS) patients. We found that, there was no statistically significant difference between the groups in terms of 25-OHD levels. However, there are several studies in the literature showing the relationship between RLS and 25-OHD levels (20-22).

In some studies, the mean of 25-OHD was showed significantly lower in the elderly persons (23-25). In this study, the median age of the control group was higher than the patient group, but the 25-OHD level was lower in the control group than the patient group. The age effect may be the reason for this result.

Table 1. Demographic characteristics of the patient and control groups

Variables	RLS Patient Group (n=21) mean ± SD	non-RLS Control Group (n=14) mean ± SD	p value
Age (year)	49.05±14.38	57.14±9.84	**0.000**
Sex (Female/Male)	15/6	11/3	**0.200**
25 hydroxyvitamin D (ng/ml)	20.06±8.79	14.75±4.67	**0.062**

*p<0.05, mean±SD; mean±standard deviation

It is known that vitamin D levels change according to the season. winter of vitamin D deficiency in a study conducted in Turkey were found to be at a higher rate (26). The inability to evaluate the seasonal variation of the 25-OHD level of the participants is one of the limitations of our study. In addition, our sample size may have limited our ability to detect differences between groups.

CONCLUSION

We did not find a significant difference between the RLS group and the control group in terms of 25-OHD levels. The cause of RLS syndrome does not seem to depend on a single parameter such as 25-OHD level. Prospective studies with larger sample groups and seasonal changes are also needed.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

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