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Original Article

Declined vitamin D may be a trigger for hemifacial spasm

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Abstract

Aim: In this study, we aimed to measure the serum vitamin D levels in Hemifacial Spasmic (HFS) patients and show the role of HFS in the pathogenesis and place in etiology.

Material and Methods: In this study, prospective 80 HFS patients and 80 healthy volunteers who were followed up at neurology clinic were prospectively included. The serum vitamin D levels of the patient and the control group with similar age, gender, and body mass index (BMI) was measured on the same day. The severity of the disease was measured using Jeong's Quality of Life Scale and correlated with vitamin D concentration. The results were compared using the independent t test and the Mann-Whitney U test.

Results: Serum vitamin D levels in patients with HFS were 16.4 [9 - 30.4] ng / ml in the patient group and 21.8 [9 - 42.6] ng / ml in the control group, and this difference was statistically significant ($p < 0.05$). There was no significant correlation between serum vitamin D deficiency and the severity of the disease and the quality of life in the patient group.

Conclusions: These results show us the role of vitamin D in the pathogenesis of HFS, the cause of which is unknown, and the importance of its location in etiology. We hypothesize that deficiency of vitamin D in HFS may lead to mechanisms that may cause to spasm starting to demyelination.

Keywords: Hemifacial Spasm; Vitamin D; Deficiency; Demyelination; Spasm Severity.

INTRODUCTION

Hemifacial Spasm (HFS) is a hyperactive facial nerve dysfunction characterized by paroxysmal, involuntary, and painless contractions that usually spread from one facet, orbicularis oculi muscle to other facial muscles (1,2). Diagnosis is based on clinical observation. Prevalence is 14.5/100.000 in women, as more dominant in women and 7.4/ 100.000 in men (3).

Vitamin D is an essential steroid prohormone, which is responsible for efficiently harvesting calcium from the diet. The primary task of vitamin D is to synergize with parathyroid hormone (Pth) in the regulation of calcium (Ca) and phosphorus (P) metabolism. This is to regulate osteoblastic activity, matrix ossification, bone turnover and bone density. However, recent studies showed that vitamin D, which acts more like hormone than vitamins, plays an important role in the function of organs outside of bone metabolism (4-5). It was reported that vitamin D has different variable roles in cell proliferation, differentiation, neurotransmission and neuroplasticity in the neurological system and has a neurotrophic and neuroprotective effect (6). However, in the literature there was no study showing a relationship with vitamin D levels in HFS patients.

Although HFS facial nerve was shown to develop due to primary and secondary damage, etiology was not fully elucidated (7). It is believed that the HFS primary causes demyelinization due to the pressure of the facial nerve root exit zone (REZ) and leads to spasm by establishing contact with the other demyelinating fibers in the axonal pathway in the fibers in this region (8). However, studies suggested that various vitamins and hormones induce degeneration of the facial nerve and demyelinization leading to ectopic excitation (9-11). As secondary cause, Bell palsy, trauma, tumor and infectious diseases are being blamed (12).

In this study, we aimed to compare the serum vitamin D levels in healthy patients with those of HFS patients and demonstrate its role in the etiology of HFS pathogenesis.

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MATERIALS AND METHODS

A total of 80 HFS patients with a total of 44 females and 36 males who were enrolled in our neurology clinic with follow-up and 80 healthy controls with age and gender similar to this disease were included prospectively between January and December 2017. Our work was carried out according to the Helsinki Declaration, with approval from the local ethics committee. Consent was received from all participants.

Demographic data such as age, gender, affected side and duration of symptom onset and number of procedures performed were recorded for all patients. The patients underwent complete neurological and ophthalmologic examination before the procedure. The body mass index (BMI) of each patient and healthy participants was calculated by dividing height by square (kg / m²).

Patients followed-up with HFS diagnosis to our clinic were included in the study at the time of the most severe spasm on the day before the last Botulinum Toxin-A (BTX-A) administration. Those with hepatic insufficiency, patients with systemic disease that would interfere with vitamin D metabolism, those taking vitamin D levels in the last 2 months, workers who would affect the level of vitamin A, and those with any neuroleptic disease were excluded from the study. In addition, MRI and MRA were taken before the study and patients with HFS due to secondary cause such as tumor, bone pathology, MS plaque which will cause HFS were not included in the study. It was identified as a control group of healthy individuals with no metabolic disease or drug trafficking that would disrupt the vitamin D level that admitted to the family medicine polyclinic and blood banking study and had similar BMI. Serum Vitamin D level of the patient and control group was measured on the same day.

Spasm severity was evaluated with Jeong's Quality of Life Scale in all of the patients. This scale consists of 2 parts. 1. The section measures the magnitude and severity of the area affected by the face half; 4 groups are divided according to the severity of the muscle group affected by the disease and the 2nd part measures the quality of daily life of the disease and consists of 7 questions that concern the daily quality. Scores from 0 to 4 are given to each question, as scores from the scale increase, daily life activities of the disease deteriorate further (13).

Sampling and Collection

Blood samples were taken between 08.00 and 09.00 in the morning after fasting all night. In our study, Architecti2000 (Abbott, Germany) device was used to measure serum 25 (OH) D levels by using chemiluminescence microparticle immunoassay (CMIA) technology. Ca, P, alkaline phosphatase (ALP), Pth, hemogram, thyroid, kidney, and liver function tests were also evaluated in patients.

Statistical Analyses

IBM SPSS for Windows version 22.0 was used for statistical analysis. Numerical variables were summarized with mean ± standard deviation or median\[minimum - maximum] values. Qualitative variables are shown in numbers and percentages. When the parametric test assumptions were met, t test was used in independent groups and Mann Whitney U test was used if there was no difference between the groups in terms of numerical variables. Whether or not there is a difference between the groups in terms of quality variables was examined by using chi square test. The relationship between numerical variables was examined by Spearman's correlation coefficient. Significance level was determined as p <0,05.

RESULTS

80 HFS patients and 80 healthy volunteers were included in the study. The mean age of the patients was 55,5 ± 12,4 and the mean age of the control group was 54,0 ± 12,6. 44 patients (55%) were in the patient group and 46 (57.5%) in the control group. The mean BMI index of HFS patients was calculated as 25.2 ± 3.1 (kg / m²) for the control group 25.8 ± 4.7 (kg / m²). Patient and control group were statistically similar in terms of age, gender and BMI (p> 0.05), (Table 1).

Table 1. Demographic data of patient and control group

	Patient (n=80)	Control (n=80)	p
Age	55.5±12.4	54.0±12.6	0.439
Gender (F/M)	44/36 (55%/45%)	46/34 (57.5%/42.5%)	0.326
BMI (kg/m²)	25.8±4.7	25.2±3.1	0.873

Mean symptom onset time was 3 [1 – 14]/months. HFS severity was 50% (40 patients) and stage 2, followed by stage 3 with 31.2% (25 patients). HFS score average was 15 [4 – 27]. During the follow-up period, BTX-A administration was performed on average 3 [1 - 20] times to patients. In patients with HFS, 52.5% (42 patients) were affected from their left facial nerve cancellous muscles more.

Serum vitamin D levels were 16.4 [9 - 30.4] ng / ml in hemifacial spasmics and higher as 21.8 [9 - 42.6] ng / ml in the control group. This difference was statistically significant (p <0.05) (Figure 1). The duration of this reduction was found as a correlation in the province (Correlation coefficient: 0.952, p=0.008).

Ca, Alp and Pth concentrations were 9,19±0,40, 74 [44 –110], 52,7 [22,5– 87,8] respectively in the patient group, and 9,48±0,34, 70 [52 – 136], 45 [16 – 86,9] respectively in the control group. In patients with HFS, serum Ca concentrations were found to be lower than the control group, and this difference was statistically significant (p <0.05). However, when groups are examined in terms of Alp and Pth concentrations; although the serum concentrations were higher in the patient group, this difference was not statistically significant (p> 0.05) (Table 2).

Table 2. Ca, Alp, Pth serum concentrations in the patient and control group

	Patient (n=80)	Control (n=80)	p
Ca (mmol/l)	9.19±0.40	9.48±0.34	<0.001
Alp (u/l)	74 [44 – 110]	70 [52 – 136]	0.491
Pth (pg/ml)	52.7 [22.–87.8]	45 [16–86.9]	0.102

There was no significant correlation between serum vitamin D deficiency HFS spasm intensity and HFS score in HFS patients (p> 0.05) (Table 3).

Table 3. HFS spasm severity and the relationship of HFS score to vitamin D deficiency in the patient group

	Spasm severity		HFS Score	
	Correlation coefficient	P	Correlation coefficient	P
Vitamin D (ng/ml)	-0.265	0.017	-0.209	0.063

DISCUSSION

In this study, we aimed to compare the serum vitamin D level in healthy control with those of HFS patients and demonstrate its role in the etiology of HFS pathogenesis. Serum Vitamin D levels in HFS patients were lower than in the control group, and this difference was statistically significant.

Hemifacial spasm (HFS) is characterized by episodic and intermittent sudden withdrawal of mimic muscles, tonic spasm and synkinesias of one side of the facial nerve. First, the periorbital is unilaterally placed and then spreads to the facial muscles of the same side over time (14). Generally, spasms tend to start in the left half of the forties when they are in the 40s and 50s and the symptoms vary in the studies done (15). In our study, we found that the average age at onset of the patients was similar to that of these studies, and the left facial nerve tended to be seen in the innerved muscles.

There are many underlying etiologic reasons for HFS. First, in 1947, Campbell et al. associated vascular abnormalities in the posterior fossa with spasms in HFS patients (12). Subsequent advances and developments in imaging and surgical techniques and the underlying etiologic cause have been advocated as facial nerve compression by ectatic vessels (16). However, in a study conducted with HFS patients, vascular abnormalities were found in 80% of patients with MRI and MRA. In the same study, a vascular abnormality was detected in 25% of the non-spasm group (17). Ridder et al. showed that vascular compression may be in any part of the cranial nerves, not just in the REZ region. These findings concluded that both vascular compression and demyelinization should be associated with hyperactivity of the facial nerve (18). In the last period, in addition to the electrophysiological and histopathological studies which are made in addition to imaging methods, two theories are being emphasized. First, there is increased neuronal excitation (ephaptic transmissions) by 'focal demyelinization' resulting in pulsatile compression in the component between central and peripheral myelin (root entry site); and the second is the pathological changes caused by the peripheral stimulation of the facial nucleus and the activation of neurons to form spasms with hyperactivity (ectopic excitation). Thus, in addition to vascular abnormalities, demyelinization of the facial nerve and associated immunological factors are associated with spasm (19-21). In HFS patients, regulation of mechanisms that regulate oxidative stress in Vitamin D, which is recently called neurosteroid, controls the level of intracellular calcium, immunological response and neurotrophic factor synthesis, regulates various proteins triggering the triggering of trigone zone, which may diminish the effects of neurodegeneration and demyelinization mechanisms. Therefore, vitamin D deficiency is considered as a factor increasing the risk of neurological diseases (22-24). We aimed to demonstrate the role of vitamin D in the pathogenesis of the HFS and HFS in etiology, which we have not studied before. However, none of the studies in the literature were found to be associated with HFS. We found vitamin D levels in our findings to be significantly lower than the control group. These results suggest that changes in vitamin D concentrations cause trigger zone demyelinization in patients with idiopathic HFS and may be one of the factors that initiate the mechanisms that trigger spasm. Our work is the first in this respect.

Vitamin D is a molecule in the steroidal structure associated with bone and calcium metabolism. Vitamin D deficiency leads to a decrease in intestinal calcium absorption and a decrease in serum calcium concentration. This causes an increase in Pth production and secretion from the parathyroid gland. PTH increases until serum vitamin D level returns to normal. The presence of vitamin D receptors in many tissues has been associated with increased interest and has led to a number of studies that have studied the relationship between various diseases and vitamin D deficiency (22). Concerning vitamin D metabolism in the brain, it has been shown that glial cells synthesize 1,25 (OH) 2D3, the active metabolite by hydroxylation by CY P24A1, a cytochrome P450 enzyme system (23-24). VDR presence was detected in brain stem, cerebellum, thalamus, hypothalamus, basal ganglion, hippocampus, and olfactory system, temporal and orbital regions. It was suggested that the neuroprotective effect of vitamin D may be demonstrated by decreasing the expression of L-type calcium channels or by increasing the level of VDR (21). In our findings, we found that serum Ca concentration, which is secondary to vitamin D deficiency in HFS, is statistically lower than control group. PTH levels that were synergistic with vitamin D and increased in concentration when vitamin D level was decreased were higher in HFS patients, but this difference was not statistically significant.

Another mechanism considered to explain the neuroprotective effect of vitamin D is that vitamin D reduces the level of reactive oxygen substrates (ROS). 1,25 (OH) 2D3 has been shown to increase antioxidant

activity in glia and neurons and reduce ROS in dead cells. It is being argued that vitamin D cannot be regarded as a vitamin only, that it plays a role in many mechanisms in the brain, and that its level is closely related to the development of some neurological diseases. It is argued that vitamin D deficiency may lead to adverse effects in the brain at various stages of life and may lead to diseases such as Parkinson's disease, Alzheimer's disease, MS, ALS (22-24). Sabchez et al. (25) that 1,25 (OH) 2D3 regulates two important molecules in the brain, glial-derived neurotrophic factor (GDNF) and neuron growth factor (NGF), and regulates the development and function of neurons in GDNF. Experimental studies have shown that demyelinization leads to motor neuron hyperactivation in some synapses of the facial nerve nucleus, in the facial nerve, and in the canine muscle (24). Dörr et al. It is stated that vitamin D is immunomodulator effect in autoimmune diseases affecting central nervous system and that vitamin D intake may slow down neurodegeneration that may occur before the onset of these diseases and reduce morbidity of the disease in later stages of the disease (26). Vitamin D deficiency in our study did not correlate with the severity of the disease. However, we argue that HFS patients may provide positive contributions to the severity of illness and daily living activities by treatment with sun exposure, which is one of the major synthetic pathways of vitamin D in the human body.

The measurement of serum 25 (OH) D concentrations is an accepted method of showing the person's vitamin D status. Pena et al. detected that vitamin D levels were higher in the summer and autumn seasons, in proportion to the incidence of solar radiation in the patient and control group (27). In our study, we found that vitamin D levels in both patient and control group were lower in the HFS group than in the control group at the same day and at the same time, in order to minimize seasonal differences. We found that vitamin D deficiency is even lower in the long-term of disease. We think that vitamin D deficiency is becoming more prominent in these patients by reducing the participation in open-air activities of social cohesion accompanying HFS and showing negative effects on diet.

The involuntary contraction of the HFS facial muscles causes pain and anxiety in the face of pain, causing sickness in people and falling in quality of life. Therefore, the presence of an etiologic cause of spasms in patients is important in terms of early treatment plan. Although there are many options in the treatment of HFS, the pathophysiology is not fully known and the ideal option is still unknown. Treatment has shown that BTX-A and microvascular surgeons are successful (20,28). However, BTX-A injection is the most commonly used treatment for HFS patients in terms of efficacy and safety. In our clinic, we diagnosed our patients and then applied BTX-A. We think that vitamin replacement in patients who have vitamin D deficiency with our study will increase the efficacy of the treatment.

Conducting our study on the volunteers with similar body mass index as the patient group is the strongest aspect of the patient and control group looking at their serum vitamin D levels on the same day. Weaknesses of our study are that 1) our study is single-centered and conducted in a small group of patients 2) HFS is a dynamic disease and therefore single measures will not provide sufficient information on serum levels.

CONCLUSION

We found that serum vitamin D levels in patients with HFS were statistically significantly lower when compared to healthy volunteers. These results show us the role of vitamin D in the pathogenesis of HFS and its importance in etiology. We think that Vitamin D deficiency in HFS can lead to neurodegeneration and the mechanisms by which spasm can lead to demyelinization. However, there is a need for more extensive studies to be done in this regard.

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