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Original Article

The effect of vitamin D levels on prognosis of patients with facial paralysis

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ABSTRACT

Objectives: This study aims to investigate the serum 25-hydroxyvitamin D3 [25(OH)D3] levels of patients with Bell's palsy (BP), and to evaluate their role in prognosis and their impact on the disease etiology.

Patients and Methods: A total of 49 patients (30 males, 19 females; mean age: 42.2±13.6 years; range, 19 to 67 years) who were diagnosed with BP and treated at our clinic between October 2019 and April 2020 were included. Blood samples were collected within 24 h after the onset of BP symptoms, and a standard oral pharmacological treatment was administered with prednisolone 1 mg/kg for 10 days and acyclovir 700 mg/day for six days. All patients were graded according to the House-Brackmann scale (HBS). The patients were divided into three groups as Grade 2, Grade 3, Grade ≥4. The patients with BP were further divided into two groups as healed (n=36) and not-healed ones (n=13). The vitamin D levels of the groups were compared.

Results: Eleven (22%) patients were in the Grade 2 group, 21 (43%) patients were in the Grade 3 group, and 17 (35%) patients were in the Grade ≥4 group. A significant decrease in vitamin D levels was observed in the patients with HBS Grade ≥4, compared to Grade 3 and Grade 2 groups (p=0.002 and p<0.001, respectively). Vitamin D levels were significantly higher among the patients without sequelae than those with sequelae (p<0.001).

Conclusion: Our study results indicate that vitamin D deficiency can affect prognosis of BP patients.

Keywords: Bell's palsy, facial paralysis, vitamin D deficiency.

Although the etiology of Bell's palsy (BP) is still uncertain, viral infections, vascular ischemia, autoimmune inflammatory disorders, and inheritance have been emphasized.[1] It is defined as unilateral paralysis or paresis and is the most common cause of all spontaneous facial paralyses, accounting for approximately half of cases.[2,3] Previous studies have reported an annual incidence of 13 to 34 cases per 100,000 individuals.[4]

Vitamin D3 is a steroid prohormone that may be taken orally and synthesized endogenously.[5] Cholecalciferol (vitamin D3) obtained from 7-dehydrocholesterol is produced endogenously using ultraviolet beams.[6]

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Vitamin D supports many basic functions in many organs, including the brain, muscles, and immune system organs. It also plays a key role in the activation of more than 200 genes.[7] Recent studies have demonstrated the distribution of 1,25(OH)2-D3 receptors (VDR) and 1 alpha-hydroxylase (1 alpha-OHase), which are responsible for producing active vitamin D3.[8] Accumulating evidence regarding VDR suggests that vitamin D3 acts like a neurosteroid.

Vitamin D3 plays an important role in the immune system, along with its classical effects on calcium and bone homeostasis; it also has effects, such as cellular differentiation and proliferation.[6,9,10] Vitamin D has been reported to assist in increasing the production of anti-inflammatory molecules and in reducing the production of pro-inflammatory molecules.[11]

Low vitamin D3 levels have been shown to be associated with the increased risk of a wide range of diseases, such as allergies, fibrotic diseases, chronic obstructive pulmonary disease, Alzheimer's disease, cancer, infectious diseases, and chronic inflammatory diseases such as obesity and diabetes.[6,12]

Studies on vitamin D3's role in neural regeneration have shown that VDR occurs in both Schwann cells,[13] as well as oligodendrocyte, and that 1,25(OH)2-D3 stimulates gene expression of neural growth factor.[14] In the present study, we hypothesized that vitamin D3 could affect prognosis of patients with BP. We, therefore, aimed to investigate the serum 25-hydroxyvitamin D3 [25(OH)D3] levels of patients with BP, and to evaluate their role in prognosis and their impact on the etiology of BP.

PATIENTS AND METHODS

This prospective study was conducted at Okmeydanı Training and Research Hospital, Department of Otorhinolaryngology between October 2019 and April 2020. A total of 49 patients (30 males, 19 females; mean age: 42.2±13.6 years; range, 19 to 67 years) who were diagnosed with BP and treated at our clinic were included. Prior to study, all patients were informed about the nature of the study and a written informed consent was obtained. The study protocol was approved by the Okmeydanı Training and Research Hospital, Ethics Committee (No: 1424). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients between 19 to 67 years of age were selected randomly into the study group, based on a consideration of exclusion criteria. Unilateral BP patients were diagnosed by ear, nose and throat and neurological examination. Blood samples were collected within 24 h after the onset of BP symptoms, and a standard oral pharmacological treatment was administered with prednisolone 1 mg/kg for 10 days and acyclovir 700 mg/day for six days. Seventeen patients who did not present a complete recovery in control visits on Day 10 and at Month 1 were referred to physiotherapy, and permanent paralysis was detected in four patients within a six-month follow-up period. Exclusion criteria were as follows: pregnancy; metabolic and neurological diseases; infection; acute or chronic infection symptoms (abnormal lymphocyte [normal: 1,000-4,800/mm^3], platelet [normal: 150,000-450,000/mm^3], and white blood cell [normal: 1,500-8,000/mm^3] counts); paralysis due to neoplastic, toxic, or iatrogenic disease; traumatic injury to the facial nerve; varicella-zoster virus infection (Ramsay-Hunt syndrome); patients whose Vitamin D treatment was initiated and was still continuing, and Melkersson-Rosenthal syndrome. According to the House-Brackmann scale (HBS), the patients were divided into three groups as follows: Grade 2 (n=11), Grade 3 (n=21), and Grade ≥4 (n=17). Levels of 25(OH)D were measured through the chemiluminescence method using the Beckman Coulter UniCel DxI 800 (Beckman Coulter Inc., CA, USA) device. Vitamin D deficiency was defined as a 25(OH)D level <20 ng/mL.[15]

Study procedure

The HBS was used for grading facial nerve owing to its simple design, frequent use, and high reliability. According to the HBS, paralysis grades are classified as Grade 1 (normal function) through 6 (complete paralysis). Each patient was evaluated on Days 1 and 10 and at Months 1, 3, and 6. Patients' medical history including diabetes, hypertension, previous herpetic

Table 1. Descriptive data of the patients

	Grade 2 (n=11)	Grade 3 (n=21)	Grade ≥4 (n=17)	
	Mean±SD	Mean±SD	Mean±SD	*p*
Age (year)	34.8±15.3[a]	42.1±13.6	47.2±10.6	0.056
25-hydroxyvitamin D	24.0±9.4[b]	18.2±6.0[b]	10.8±4.4	<0.01*

SD: Arithmetic mean ± standard deviation p<0.05; statistically significant; * p value was calculated through one-way ANOVA analysis; a: Comparison with Grade ≥4 p<0.05; b: Comparison with Grade ≥4, p<0.01.

infections, systemic infections, autoimmune disorders, sound-vestibular symptoms, and family history of facial paralysis was obtained.

The following tests were ordered for patients with HBS Grade ≥4, as well as the patients who presented with no improvement after treatment on Day 10 as assessed by cranial magnetic resonance imaging with gadolinium, audiometric, and impedance tests and electromyography, electroneurography, and eye-blinking-reflex electrophysiological tests. Physiotherapy was recommended to the patients with HBS Grade ≥4 who did not present any clinical improvement at the end of Month 1.

Serum 25(OH)D concentrations between 20 and 40 ng/mL (50 to 100 nmol) were considered normal, whereas levels below 20 ng/mL were considered deficient.[10] The patients in the study group (Vitamin D-deficient patients) received standard therapy with a loading dose of 50,000 IU cholecalciferol per week for a total of eight weeks, followed by 1,500 IU maintenance therapy.

RESULTS

There was a statistically significant difference in the age between the Grade 2 and Grade ≥4 groups (p<0.05) (Table 1). Eleven (22%) patients were in the Grade 2 group, 21 (43%) patients were in the Grade 3 group, and 17 (35%) patients were in the Grade ≥4 group. Changes in 25(OH)D levels were analyzed in all the groups. The mean 25(OH) D levels were 10.8±4.4 for the Grade ≥4 group, 24.0±9.4 for the Grade 2 group, and 18.2±5.9 for the Grade 3 group. A significant decrease in vitamin D levels was observed in patients with HBS Grade ≥4 (p=0.002 and p=0.000, respectively) (Table 1, Figure 1). However, a comparison of mean vitamin D levels by sex revealed no significant difference for vitamin D levels between male (15.5±7.5) and female (19.2±8.7) patients (p=0.115 and p>0.05, respectively). The Patients with BP were further divided into two additional groups as healed (n=36) and non-healed ones (n=13). Vitamin D levels were significantly higher in the patients without sequelae than those with sequelae (p<0.001) (Table 2).

DISCUSSION

Bell's palsy progresses with ischemia and demyelination of the facial nerve at the ganglion level. This inflammatory process of the facial nerve persists indefinitely.[16] Although idiopathic BP is rarely bilateral, it appears with a complete or partial loss of mobility on one

Table 2. 25-hydroxyvitamin D levels between two groups (complete recovery and incomplete recovery)

	25-hydroxyvitamin D	
	Mean±SD	*p*
Completely healed (n=36)	20.7±7.3	<0.001
Not completely healed (n=13)	9.7±3.0	

SD: Standard deviation.

side of the face in most cases. Early treatment is recommended to prevent pathophysiological processes, such as viral replication and ischemia in the facial nerve, which are thought to play a role in the etiology of BP.[3] The actual purpose of treatment is to accelerate recovery and prevent corneal complications. The BP presents a high prevalence of spontaneous recovery;[17] however, treatment is performed with high-dose corticosteroids, the efficiency of which has been proven in a limited pattern, and antiviral agents of conflicting therapeutic efficiency.[4]

In the present study conducted in patients diagnosed with BD, we examined 25(OH)D levels by dividing patients into groups according to disease stage. We detected vitamin D levels to be significantly lower in HBS Grade ≥4 patients, compared to the other patients. On the other hand, we found that the initial vitamin D levels of the patients who did not show complete recovery during their follow-up were significantly lower than the patient group with complete recovery (Table 2).

Various immunological studies have been conducted to demonstrate the link between vitamin D and the immune system.[18,19] *In vitro* studies have shown that prohormone D3 is perceived by innate immune receptors, and 1,25(OH)2D3 increases hypersensitivity to pathogen-associated molecular patterns (PAMP) by downregulating TLR2 and TLR4 expression on the monocytes involved in the immune mechanism.[20] Moreover, 1,25(OH)2D3 has been observed to increase the expression of the trigger receptor (TREM-1) expressed on myeloid cells-1 in human monocytes and macrophages.[21]

Furthermore, the association between several important neurological diseases and lower vitamin D levels are supported by *in vivo* and *in vitro* studies.[22] In their animal study, Cabas et al.[23] observed that vitamin D3 (cholecalciferol) administered after left peroneal nerve incision induced locomotor and electrophysiological recovery in the nerve. Furthermore, cholecalciferol was shown to increase the axon count, diameter, and neuritis myelinization.

In the etiology of BP, inflammation, as well as degeneration of the edematous perineurium and myelin sheath have been identified between the nerve fibers and blood vessels in a facial nerve biopsy, and this finding is compatible with herpes zoster infection, which is a viral infection.[24] However, viral infections, including other viral pathogens such as cytomegalovirus, rubella virus, mumps virus, influenza B virus, and coxsackie virus, were also reported to be rarely involved.[25] Vitamin D has been also shown to reduce replication of viral agents, such as respiratory syncytial virus and rotavirus by regulating antimicrobial peptides such as cathelicidin and beta-defensin.[26,27] Studies in the literature have suggested that adequate vitamin D levels may prevent facial paralysis and reduce the disease's severity.

Vitamin D deficiency is observed in individuals with advanced age, obesity, sun avoidance, residence at northern latitudes, and darker skin tones.[28] In our patient group, the prevalence of vitamin D hypovitaminosis was expected, as all the patients in our study group were living between 36° and 42° northern latitudes and 26° and 45° eastern longitudes in the autumn-spring period.

Vitamin D levels were significantly lower in patients with prolonged healing and sequelae in this study. We believe that lower vitamin D levels may affect nerve regeneration in the grade and progression of BP. Therefore, vitamin D prophylaxis (without overdosing) may contribute to reducing BP severity, particularly in settings where hypovitaminosis D is common. The use of vitamin D for prophylaxis by those with any concomitant gastroenterological diseases, living in regions where vitamin D deficiency is common, may also be useful in BP, as in other metabolic diseases.

The main limitations of the present study are its relatively small sample size and different duration of patients' sun exposure or sun protection status depending on cultural and social differences, and patients' age (known to affect sensitivity to vitamin D deficiency). Another limitation is the lack of analysis of inflammation markers.

In conclusion, Vitamin D may protect against peripheral facial paralysis and accelerate healing through its preventive effect against viral infections and its neuroprotective effect.

Furthermore, it may accelerate the recovery period for facial neural functions in patients with BP. Our results may contribute to this evidence and support public health measures, including dietary supplements, to improve vitamin D status, particularly in settings where significant vitamin D deficiency is common. However, further large-scale, prospective, randomized studies are needed to more accurately interpret the relationship between 25(OH)D3 deficiency and inflammation.

Declaration of conflicting interests

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