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The effect of vitamin D deficiency in patients with trigeminal neuralgia: A case control study

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Abstract

An association between vitamin D deficiency and chronic pain has been suggested in several observations. The objective of this study was to determine whether there was an interrelation between patients with trigeminal neuralgia and vitamin D levels. This study included 45 patients. All patients were diagnosed with trigeminal neuralgia in the Department of Pain Management. Age, sex, diagnosis year, antiepileptic drug use and medication for trigeminal neuralgia (TN) treatment were obtained and recorded. Patients included in the study were grouped based on the Barrow Neurological Institute Pain lntensity Scale (BNI) as BNI <4 Group 1, BNl > 4 Group 2. Trigeminal neuralgia patient's quantitative assessment of pain was performed under the supervision of a pain specialist who was blinded to the study. Demographic data were similar in each group. A patient in Group I and 13 patients in Group 2 had interventional pain therapies before blood samples were obtained. The mean level of vitamin D was found as 29.6 + 5.8 ng/ml in Group I and defined as insufficient. The mean level of vitamin D was 12.9 + 5.0 ng/ml in Group 2. The mean level of Vitamin D was significantly lower in patients with a BNI pain intensity value ≥4 ($p < 0.001$). lt is concluded that decreased serum vitamin D concentration was associated with trigeminal neuralgia. Although it is not easy to determine any causal correlation with a cross-sectional case control study, we concluded that vitamin D deficiency, as a risk factor for many acute and chronic diseases, was associated with pain severity in trigeminal neuralgia patients.

Keywords: Trigeminal Neuralgia, Trigeminal Nerve, pain, Anticonvulsants, headache, vitamin D, vitamins, BNI

Introduction

The lesions in the peripheral or central nervous system cause chronic neuropathic pain in various forms which is still difficult to fully understand the underlying mechanisms. Trigeminal neuralgia is a sudden onset paroxysmal severe headache in a lightning flash type and its pathophysiology is not fully understood for the time being [1]. The trigeminal neuralgia afflicts one or two branches, commonly the second and third division of the trigeminal nerve. lt is usually unilateral and occurs in the middle ages [2]. The prevalence of TN is approximately 0.07% and constitutes 2% of facial pain [3], and nearly twice as common in women than men [4].

The most accepted pathophysiological mechanism of trigeminal neuralgia is impulse activity originating in the peripheral aspects of the trigeminal system hypothesis proposed by Devor and his colleagues [5]. The compression or demyelination of afferent neurons in the trigeminal nerve or ganglion is another possible mechanism [6]. This pathological condition permits spontaneous ectopic generative impulses and abnormal nonsynaptic ephaptic transmission to adjacent fibers of the nerves. A-Beta and A- Delta fibers subserving light touch and pain closest in proximity within the root entry zone are causing the paroxysmal pain provoked by cutaneous stimuli. A nerve section pathologic examination reveals the apposition of demyelinated axons [7, 8].

The role of vitamin D was thought to be confined to calcium, phosphate and bone mineralization and maintenance for several decades [9]. Current evidence suggests that there is a broader biological role of vitamin D3 in tissues not primarily associated with mineral metabolism [10]. Also, disruption of calcium homeostasis in neurons caused by long term deficiency of vitamin D increases neurodegeneration causing the vulnerability of neurons to aging [11]. Accordingly, many chronic diseases such as infectious and autoimmune diseases, cancers, cardiovascular diseases, and metabolic syndrome have been revealed to be associated with vitamin D deficiency, in recent years [12, 13]. The relation between vitamin D deficiency and amyotrophic

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lateral sclerosis (ALS), multiple sclerosis (MS), atherosclerosis, inflammatory bowel disease and diabetes mellitus (DM) has recently been reported [14].

Studies have proposed a relationship between vitamin D deficiency and chronic pain [15, 16]. The incidence of vitamin D deficiency is very high among the general population. Up to now, no data on the association between vitamin D deficiency and trigeminal neuralgia are present in the literature. The primary objective of the study was to determine the association between serum levels of vitamin D and pain intensity of trigeminal neuralgia patients. Other secondary aims were the measurement of vitamin D related electrolytes and hormones.

Materials and Methods

This case control study included 45 patients. The diagnoses of all patients were established following the diagnostic criteria for trigeminal neuralgia with the International Classification of Headache Disorders [17]. All patients diagnosed as trigeminal neuralgia in the Department of Pain Management, Turgut Ozal Medical Center of lnonu University. Before the beginning, the study protocol was approved by the local Ethics Committee of lnonu University (IRB 2018/164). All patients were informed about the objectives of the study and gave written informed consent.

The patients who were diagnosed with trigeminal neuralgia were invited to our Pain clinic, the intensity of pain was measured and blood samples were obtained following March 2018 to April 2019. The intensity of the pain in patients with trigeminal neuralgia was evaluated with Barrow Neurological Institute (BNI) Pain Intensity Scale [18] (Table 1), which is frequently used to evaluate pain as a subjective complaint and visual analog scale. The former gives additional qualitative information on the intensity of pain and the need for medication and the latter rates the pain intensity between 0 (no pain) and 10 (the worst pain that can be imagined). Patients were divided into 2 groups according to the BNI Pain Intensity Scale as BNI <4 in Group 1, BNI ≥4 in Group 2. Primary trigeminal neuralgia patient's quantitative pain assessments were performed under the supervision of a pain specialist who was blinded to the study.

The disease duration was longer than 2 years in all patients. The inclusion criteria were unilateral pain within the distribution of the trigeminal nerve; paroxysmal electric-like or stabbing pain that is evoked by stimuli; and no sensory loss or neurological deficits. Patients with a history of acute or chronic diseases, including chronic liver disease, bone disease, chronic renal failure, primary hyperparathyroidism, Cushing's disease, chronic diarrhea, pregnancy, and the patients who had taken vitamin D supplementation within the previous 4 weeks were excluded from the study.

Age, sex, year of diagnosis, antiepileptic drug use, interventional procedures were questioned and recorded for all patients. The patients who had smoked one and more cigarettes per day during the last year were defined as smokers and consumed alcohol was considered drinker. The amount of alcohol intake in our country is difficult to determine as this information is rarely revealed.

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Table 1. BNI (Barrow Neurological Institute) Pain Intensity Scale

I	No pain, no medical treatment
II	Sometimes partial pain, no need for medical treatment
III	Partial pain, adequate pain control with medical treatment
IV	Partial pain, no pain control with medical treatment
V	Severe pain, no pain control

25 (OH) Vit D3 levels were measured from blood samples obtained from the non-fasting patients. According to the Turkish Osteoporosis and Metabolic Bone Diseases Diagnosis and Treatment manual published in 2017 by the Turkish Society of Endocrinology and Metabolism, serum 25 [OH] D levels have evaluated in 4 categories; I. Severe deficiency group (those with Vit D level < 10 ng / ml), II. Deficiency group (those with Vit D level 11-20 ng/ml), III. Risk of deficiency group or insufficiency group (those with Vit D level 21-30 ng/ml) and IV. Normal group (those with a vitamin D level > 30 ng/mL) [19]. Sunlight exposure was not assessed for the patients included in the study due to the various limitations such as patients from different altitudes and clothing styles.

The prevalence of trigeminal neuralgia is about 0.7% in the general population. To detect an effect size of 0.10 at the alpha error of 0.05 and statistical power of 0.80, the calculated sample size was 36 matched pairs.

SPSS for Windows statistical program (version 18, IBM Inc, Chicago, Ill, USA) was used in statistical analysis. Categorical variables were expressed as number and percentage, and continuous variables as mean ± standard deviation. The normality of data was reviewed using the Anova or Kruskal-Wallis tests. Continuous variables were compared with unpaired t-test or Mann Whitney U test; categorical variables were compared with the chi-square or Fisher exact test, according to the distribution. Spearman correlation analysis was performed to determine the potential relationship between BNI PainIntensity Scale and serum 25 [OH] Vit D values. The significance level was accepted as $p < 0.05$ in all statistical analyses.

Results

Forty-five patients who applied to the polyclinic with the diagnosis of trigeminal neuralgia were examined. Five patients with chronic liver disease, brine disease . cronic renal failure, primary hyperparathroidism, Cushing's disease, cronic diarrhea, and pregnancy were excluded from the study. When 39 patients were classified according to BNI scoring, it was seen that the number of patients was 13 in Group 1 and 26 in Group 2 (Figure 1).

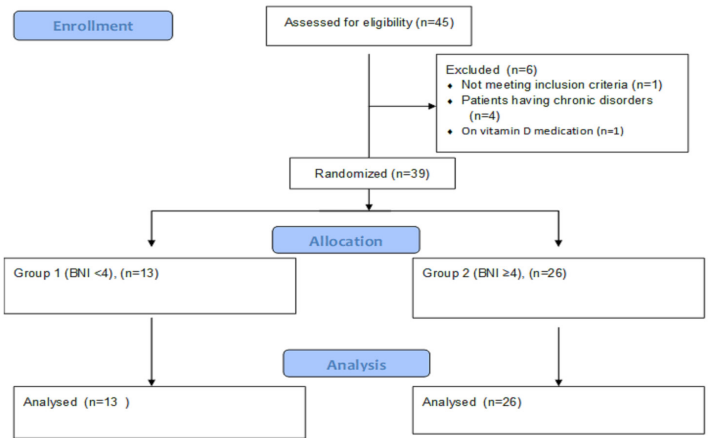

Figure 1. Of 45 patients were rewieved. 6 patients were excluded from the study. Patients were divided into 2 groups according to BNI Pain Intensity Scale as BNI <4 in Group 1, BNI ≥4 in Group 2

The mean age, gender, and duration of the disease were similar in both groups (Table 2). All patients were on antiepileptic drugs in Group 1 , and 2 patients had no antiepileptic drug in Group 2. No MS patient was detected in our patients' groups.

One patient in Group 1 and 13 patients in Group 2 had interventional procedures in the pain clinic. The medication regimens were not uniform for Group 1 and Group 2 patients. Most of the patients were using carbamazepine for pain control, and some were using phenytoin, oxcarbazepine, gabapentin or pregabalin. A few patients even tried different forms of herbal medicine (Figure 1). Characteristics of the patients and pain intensity, visual analog scale (VAS), Vitamin D levels, laboratory results were shown in Table 2.

Primary outcome

The mean Vitamin D level was 29.6 ± 5.8 ng/ml in trigeminal neuralgia patients with BNI < 4 and it was concluded that there was vitamin D deficiency. In patients with partial pain without adequate pain control with medical treatment, and patients with severe pain, the mean vitamin D level was 12.9 ± 5.0 ng/ml and vitamin D deficiency was observed. Vitamin D levels in Group 1 were significantly lower than Group 2 ($p < 0.001$) (Fig. 2).

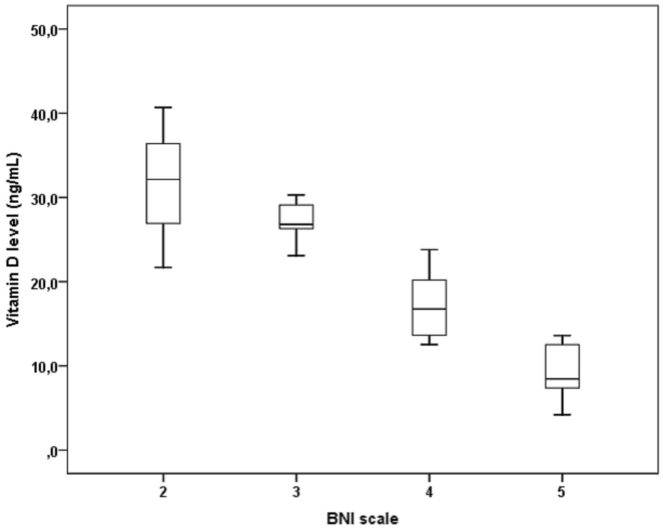

Figure 2. O Association between vitamin D level and Barrow Neurological Institute Pain Intensity Scale. Pain intensity was scaled as I = No pain, no medical treatment, II = Sometimes partial pain, no need for medical treatment, III = Partial pain, adequate pain control with medical treatment, IV = Partial pain, no pain control with medical treatment, V = Severe pain, no pain control. A significantly negative correlation was observed between vitamin D level and BNI score ($r= -0.929$, $p < 0.001$).

Table 2. Characteristics of the patients and Pain Intensity (Visual Analog Scale), vitamin D levels, laboratory result

	Group 1 (BNI < 4) (n=13)	Group 2 (BNI ≥ 4) (n=26)	P value
Age, yr	56.2±8.4	53.2±12.6	0.433
Sex, male, n, %	7 (%53.8)	10 (%38.5)	0.361
Disease Duration, yr	5.3±3.0	6.7±5.6	0.417
Blocking, n, %	1 (%7.7)	13 (%50)	0.009
Creatinin, mg/dL	0.8±0.1	0.8±0.1	0.514
Albumin, g/dL	4.2±0.5	4.2±0.4	0.952
Calcium, g/dL	9.2±0.6	9.1±0.7	0.844
Phosphorus, mg/dL	3.6±0.7	3.4±0.6	0.359
PTH, pg/mL	32.0±16.5	36.5±15.9	0.422
Vit D level, ng/ml	29.6±5.8	12.9±5.0	<0.001
BNI score	2.7±0.5	4.5±0.5	<0.001
VAS Score	3.0±1.68	6.5±2.04	<0.01

Secondary outcome

The mean phosphorus level was significantly lower, and the PTH level was significantly higher in Group 2. There was no significant difference in creatinine, albumin, and calcium levels between groups.

Discussion

Although there are many hypotheses about the etiology and pathophysiology of trigeminal neuralgia, there is no definite conclusion. Lewy et at. [20] emphasizing that small vascular events may cause this disease. Knight [21] has shown that herpes simplex

infections caused chronic damage in the ganglion. In another study, it was argued that the cause of the pain was the pathological multineural reflex in the trigeminal system. Of all the theories, vascular pressure theory is the most supported one. According to this theory developed by Jannetta [22], he emphasized that the transition region of central and peripheral myelin may be the cause of this neuralgia. Fromm et al. [23] combined central and peripheral theories and emphasized that damage to the trigeminal nerve root causes central synaptic changes is the reason caused trigeminal neuralgia.

Vitamin D deficiency is now a global problem and it has been determined that the risk of vitamin D deficiency is 51.8% and vitamin D deficiency is 20.7% among the Turkish population [24]. Vitamin D deficiency caused by poor exposure to sunlight, malabsorption, increased catabolism due to various drugs such as phenytoin and phenobarbital, and in infants with prior vitamin D breastfeeding. Other factors affecting the level of vitamin D were ethnicity, skin color, season, clothing style, age, gender, and a residency [25]. In our study, age, gender, and antiepileptic drug use were similar in both groups. Both patients were living in the same province with hot-dry climate, latitude, and longitude at 38° East 38° North. Ethnicity and skin color were similar in each group of our study.

Fat tissue, pancreas, skin, endothelium, smooth muscle, myocardium, brain, placenta, breast, prostate, ovarian, pituitary, immune cells, and colon cancer cells have vitamin D receptor [15, 26]. In addition to the immunomodulatory effect of vitamin D, it has other non- immunomodulatory actions. Among vitamin D's diverse extra-skeletal effects, this vitamin enters the neurons, oligodendrocytes, microglia, and astrocytes, and it could exert other modes of action such as remyelinating, neuroprotector, neurotrophic effects, etc. [27] and a link between axonal degeneration and vitamin D deficiency seems to exist in multiple sclerosis patients [28]. Vitamin D inhibits nitric oxide synthase and decreases the synthesis of nitric oxide, which affects neurotransmission and vasodilation. Modulating receptors and neurotransmitters like dopamine, acetylcholine, gamma-aminobutyric acid, N methyl D aspartate and serotonin are other mechanisms of vitamin D on neural pathways. Positive effects of vitamin D on the neural growth factor, contribute to the growth, maintenance and protection of sensory and sympathetic neurons in the central nerve system. In addition, Vitamin D upregulates TGF-β1 and interleukin-4 and subsequently suppresses cytokines such as interferon-gamma, TNF-α, interleukin-1, and interleukin-2, which are the mediators of inflammation [29].

Many studies emphasize the importance of vitamin D in neurological diseases. As it is known, the relation between bilateral trigeminal neuralgia and multiple sclerosis has been demonstrated [30]. Vitamin D deficiency is associated with pain in patients with high pain severity, which suggests that there is a relationship between pain severity and trigeminal neuralgia mechanism in patients with multiple sclerosis. As recently confirmed in numerous immunological studies performed in multiple sclerosis patients the incidence of this disease in the community can be explained by a low 25 (OH) D3 level and that vitamin D deficiency is a risk factor in the development of multiple sclerosis [31]. Vitamin D intervenes in multiple sclerosis, which vitamin D supplementation resulted in multiple beneficial immunological effects in multiple sclerosis patients [32] and positive effects were detected approximately 50% of patients treated with vitamin D in multiple sclerosis patients [33]. lt has been emphasized that vitamin D has an immunomodulatory effect that inhibits sclerosis formation and slows neurodegeneration and affects morbidity [34]. Wergeland et al. [35] claim that vitamin D reduces the demyelination and microglia activation/macrophage infiltration independent from central nervous system leukocyte infiltration in MS-modeled mice. Also in several cases, stimulation of neurotrophin production by 1,25-(OH) D3, which is correlated with a neuroprotective effect has been documented [36,37]. The most recent findings linking antiepileptic medication and vitamin D insufficiency is recently published by Yildiz et al [38].

This study has several limitations. This observation was performed with convenience samples in a single pain clinic. Therefore, as it cannot truly represent trigeminal neuralgia patients all over the world, these observations cannot be generalized, due to its single-center nature; and thus there is a need for further multicenter studies. Serum levels of vitamin D vary by many factors; therefore, further multicentric studies are needed to find out whether these results apply in different settings. Although the most common causes of secondary generalized pain were excluded by taking a good medical history, physical examination, and investigations; the possibility of other causes of secondary trigeminal neuralgia pain cannot be completely ruled out.

As emphasized in the studies, vitamin D deficiency which is associated with many diseases has been a guide to our study. In our study, we found that the levels of vitamin D in patients with severe trigeminal neuralgia were low. We think that the studies on this issue should be replicated with larger groups and further multicenter studies are needed to draw a final decision.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

All authors declare no financial support.

Ethical approval

Before the beginning, the study protocol was approved by the local Ethics Committee of lnonu University (IRB 2018/164).

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