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Original Article

Comparison of Serum Concentration of Ca, P, Mg, and Fe between Hemifacial Spasm Patients and Healthy Controls; Prospective Randomized Controlled Study

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Abstract

Purpose: In this study, we aimed to measure the serum vitamin D level in hemifacial spasmic (HFS) patients and show the role of HFS in the pathogenesis and place in etiology. **Materials and Methods:** This study included 43 prospective newly diagnosed HFS patients and 43 healthy volunteers in the neurology clinic. The serum (Ca, P, Mg, Fe) concentration of 4 essential elements was measured with a biochemical device. The groups were correlated in terms of four essential element concentrations. The severity of the disease was measured using Lee's Quality of Life Scale and correlated with the concentration of four trace elements. The results were compared using the independent *t*-test and Mann–Whitney U-test. **Results:** Concentration of serum Ca, P, and Mg in the HFS patients was found to be lower in the control group which was statistically significant ($P < 0.05$). There was no statistically difference between the groups in terms of Fe concentration ($P > 0.05$). There was no significant correlation between trace element concentration and severity of illness and daily life quality in the patient group. **Conclusion:** These results show us the role of HFS in the pathogenesis of these four trace elements and the importance of its location in etiology. We think that changes in the concentration of trace elements in HFS can lead to demyelinization, which may lead to spasm.

Keywords: *Calcium, hemifacial spasm, iron, magnesium, phosphorus*

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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.[1-3]

Although HFS facial nerve was shown to develop due to primary and secondary damage, etiology was not fully elucidated.[4] It is believed that the HFS is primarily caused by the pressure of the facial nerve in the root exit zone (REZ).[5] However, studies suggested that ectopic excitation is the primary cause of facial nerve demyelinization, in which it is insufficient to connect the disease with only norovascular causes.[6-8] As secondary cause, Bell palsy, trauma, tumor and infectious diseases are blamed.[9]

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The changes in trace element concentrations are associated with many neurodegenerative and demyelinating neurological disorders.[10] Recent studies in HFS suggested that changes in the serum concentration of four trace elements (Ca, P, Mg, and Fe) cause demyelinization in the facial nerve, thereby increasing neuronal hyperactivity and triggering spasm.

In this study, we aimed to compare serum Ca, P, Mg, and Fe concentration in HFS patients with those of

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healthy individuals to show the role of HFS patagonia and its role in etiology.

Materials and Methods

Prospectively, 23 male and 20 female patients with a total of 43 HFS patients who were referred to our neurology clinic and 43 control cases with age and sex similar to this disease were included in this study. Our study was carried out according to the Helsinki Declaration, with approval from the local ethics committee. Consent was obtained from all participants.

Demographic data such as age, gender, affected side, and duration of onset of symptoms 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 participant was calculated by dividing the height value by its square (kg/m²).

Patients who were admitted to our clinic with HFS pre-diagnosis and diagnosed as HFS were included in the study. Those who have systemic disease that will interfere with the metabolism of liver, liver failure or Ca, P, Mg, and Fe, those who will disrupt these four trace element metabolism in the last 2 months will affect the level of the worker, those who work, and those with any neurological disease. In addition, magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) were taken before the study, and HFS due to secondary cause such as tumor, bone pathology, Multiple Sclerosis (MS) plague, which would cause HFS were not included in the study. It was identified as a control group of healthy individuals who did not have any metabolic disease or drug intake traumas that would interfere with the metabolism of Ca, P, Mg, and Fe metabolism that admitted the family medicine physician and the blood bank.

Spasm severity was evaluated with Lee's Quality of Life Scale in all patients. This scale consists of two parts. The first section measures the magnitude and intensity of the area affected by the face half, according to the severity of the muscle group affected by the disease and separated to four groups according to disease severity and second part measures the quality of daily life of the illness and consists of seven questions that concern the daily activities. Each question is scored from 0 to 4, and as the score from the scale increases, the severity of the disease increases.[11]

Sampling and collection

The concentrations of four essential elements were measured with Olympus AU400 automatic biochemistry analyzer.

Statistical analyses

SPSS software version 22.0 (IBM Corp., Armonk, NY, USA) 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 the square test. The relationship between numerical variables was examined by Spearman's correlation coefficient. Significance level was determined as $P < 0.05$.

Results

Forty-three HFS patients and 43 healthy volunteers were included in the study. The mean age of the patients was 53.8 ± 14.0 years, and the mean age of the control group was 53.5 ± 13.9 years. In the patient group, 23 patients (53.5%) in the control group and 25 (58.1%) in the control group were males. The mean BMI index of HFS patients was calculated as 25.5 ± 3.0 (kg/m²) for the control group which was 25.9 ± 3.7 (kg/m²). Patient and control groups 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*=43)	Control (*n*=43)	*P*
Age	53.8±14.0	53.5±13.9	0.920
Gender (male/female)	23/20 (53.5%/46.5%)	25/18 (58.1%/41.9%)	0.828
BMI (kg/m²)	25.9±3.7	25.5±3.0	0.587

BMI=Body mass index

Table 2: Concentration of Ca, P, and Mg elements in patient and control group

	Patient (*n*=43)	Control (*n*=43)	*P*
Ca mmol/l	9.2±0.4	9.5±0.4	0.002*
P mmol/l	3.0±0.4	3.2±0.6	0.018*
Mg mmol/l	2 (1.5–2.5)	2.2 (1.5–2.5)	0.025*

Table 3:The severity of hemifacial spasm spasm and the relation of daily quality of life to trace elements in the patient group

	HFS spasm intensity		HFS daily life quality
	Correlation coefficient	*P**	Correlation coefficient
Ca	0.016	0.921	0.044
P	0.006	0.968	0.046
Mg	0.073	0.643	−0.013
Fe	0.068	0.665	−0.030

**P* (Pearson correlation coefficient). HFS=Hemifacial spasm

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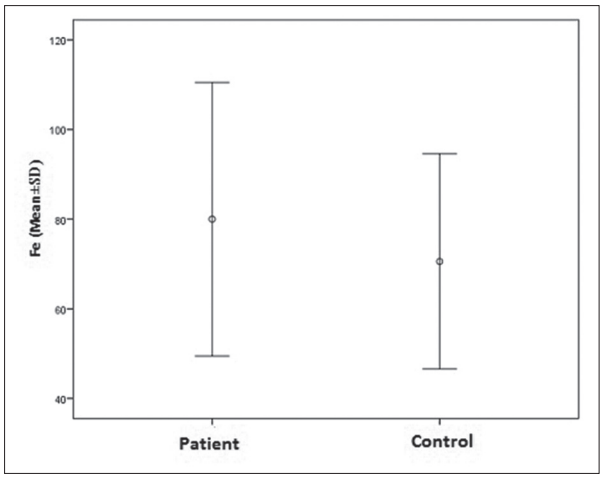

Figure 1: Serum Fe concentration values of hemifacial spasm and control group

Mean symptom onset time was 4 [1–24]/months. The mean HFS severity score was 15.6 ± 5.1 and the HFS magnitude was 58.1%. This was followed by stage 3 with 34.9%. In patients with HFS, 58.1% (25 patients) and more right facial nerve cancers were affected.

The concentrations of Ca, P, Mg, and Fe in the patient 9.2 ± 0.4, 3.0 ± 0.4, 2\[1.5–2.5], 70.6 ± 24.0 mmol/l group were, respectively, 9.5 ± 0.4, 3.2 ± 0.6, 2.2 ± 1.5–2.5, 80.0 ± 30.5 mmol/l. Concentration of serum Ca, P, and Mg in HFS patients was found to be lower than control group and this difference was statistically significant ($P < 0.05$). However, when the groups were examined in terms of Fe concentration, the Fe concentration was higher in the patient group, but there was no statistical difference ($P > 0.05$) [Table 2 and Figure 1].

When the four elements of HFS were compared with the HFS spasm intensity and daily quality of life, it was found that there were no four-element had no correlations ($P > 0.05$) [Table 3].

Discussions

In this study, we aimed to compare the serum Ca, P, Mg, and Fe concentration in HFS patients with those of healthy individuals and to show the role of HFS pathogenesis and its role in etiology. Serum Ca, P, and Mg concentration was lower than control group and this difference was statistically significant. Fe levels were higher in the patient group, but this difference was not statistically significant.

Trace elements are the building blocks of the enzymatic system and horns in the human body and have important tasks in the transport and use of proteins in the target organ.[12] Changes in the level of trace elements lead to the formation of many metabolic and neurological diseases. Recently, trace element deficiency was associated with a number of neurodegenerative and demyelinating neurological disorders such as Alzheimer's, Parkinson's, multple sclerosis (MS), trigeminal neuralgia (TN), and the number of related studies is rapidly increasing.[6,9,10] However, none of the studies in the literature were found to be associated with HFS. Our work is the first in this respect.

HFS is characterized by episodic and intermittent sudden withdrawal of tonic muscles, tonic spasm, and syneresis of one side of the facial nerve. First, the periorbital is unilaterally placed, and then spread to the facial muscles of the same side over time. Diagnosis is based on clinical observation. Prevalence is 14.5/100.000 to be dominant in women and 7.4/100.000 in men.[13]

There are many underlying etiologic reasons for HFS. First, Campbell and Keedy associated vascular anomalies in the posterior fossa with spasms in HFS patients in 1947.[9] Subsequent advances and developments in imaging and surgical techniques and the underlying etiologic cause were advocated as facial nerve compression by ectasic vessels.[14] However, in a study with 34 HFS patients, vascular abnormalities were detected in 80% of patients with MRI and MRA. In the same study, 25% of vascular abnormalities were detected in the nonspasm group.[14] Recently, two theories were emphasized with the electrophysiological studies. First, there is increased neuronal excitation 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. Thus, in addition to vascular abnormalities, demyelinization of the facial nerve, and associated immunological factors are associated with spasm.[15,16] In our work, we supported this hypothesis by investigating whether the changes in trace element concentration are secondary to demyelinization and whether it has a trigonal zone effect compared to healthy individuals.

The involuntary contraction of the HFS facial muscles causes pain and stress and anxiety in the socially people and causes a decrease 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 with botilinium toxin injection (BTX-A) and microvascular surgeon was shown to be successful.[17,18] However, BTX-A injection is the most commonly used treatment for HFS patients in

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terms of efficacy and safety. In our clinic, we diagnosed our patients and then applied BTX-A.

Relationship between Ca, P, and hemifacial spasm

There are many functions in neuromuscular functions such as calcium muscle contraction and nerve conduction, fibrin formation in the coagulation cascade, intracellular and extracellular signaling, and hormone secretion.[19] It also helps bone mineralization. Osteoporosis and bone fractures occur without it. P is important for bone mineralization, skeletal development, and intracellular metabolism. Serum Ca levels are closely associated with P. In both cases, both is absorbed from jejunum and stored in the bones. The metabolism of these trace elements is regulated by calcitonin. Previous studies in the literature have not found a study showing local chemical changes leading to hyperexcitability of the facial nerve. However, the amount of Ca in neuronal tissues exposed to oxidative stress has been shown to decrease.[20] Zhao *et al*. found that serum Ca and P levels were lower in TN patients in their study when compared to healthy volunteers in serum Ca and P levels. They argued that these low-level trace elements lead to demyelination in the nerves, and they associate it with TN pathophysiology. In addition, visual aggression scores (VAS) measured the severity of neuralgic aggression in the stomach, and this decrease was found to be strongly correlated with the severity of the pain.[21] There was no study of serum Ca and P concentration in patients with HFS in the screening of literarture. In our study, we found serum Ca and P concentrations statistically lower in HFS compared to controls, but this low level did not correlate with spasm intensity and HFS daily quality of life. We associated this change in Ca and P concentration to the fact that facial nerve can initiate the mechanisms that trigger demyelinization.

Relationship between Mg and hemifacial spasm

Mg is the most abundant element in the cell after potassium and is one of the trace elements that plays an important role in human physiology. Cell proliferation and differentiation are involved in nucleic acid synthesis and protein metabolism.[22] It is also involved in energy transfer and storage, cellular respiration, and nerve impulse transmission. MG deficiency was associated with many neuropsychiatric disorders such as Alzheimer's, anxiety, depression, Parkinson's, and MS. After experimental spinal cord ischemia he improved neurological dysfunction with Mg treatment. The neuroprotective effect of Mg is explained by the vasodilatation of the increase in blood flow and the protection of neurons by inhibition of cell death by preventing intracellular Ca accumulation.[23] Alizadeh *et al*. found serum Mg concentration to be lower than in the control group and relate it to demyelinization in their study of patients with MS.[6] In our study, we considered the serum Mg concentration to be statistically low in HFS as one of the causes of demyelinization.

Relationship between Fe and hemifacial spasm

Iron is an essential element due to the need for erythropoietic function, oxidative metabolism, and cellular immunity. Iron is the most abundant metal and has many vital cellular functions such as neurotransmitter synthesis, myelinization, and mitochondrial function. Numerous neurological diseases have been associated with the iron level in the CNS, but the exact cause has not been found.[24,12] Aspli *et al*. found that apoptosis caused by oxidative stresses in high Fe-level neurons and alterations in the serotonergic and dopaminergic cortical network system lead to dmyelinase by binding to various proteins. Thus, they believe that the pathogenesis and progression of the disease is accelerated.[25,26] We found that Fe concentration in our study was higher in the HFS group than in the control group, but this difference was not statistically significant.

It is the strength of our study to be carried out in a newly diagnosed group of patients who have not previously undergone any medical or surgical treatment and to be conducted on volunteers with a similar body mass index to the patient group. The weaknesses of our study are: (1) our work is single-centered and carried out in a small group of patients, (2) our work has four main trace elements and is not combined with other trace elements, (3) HFS is a dynamic disease, and therefore, a single measure can not provide sufficient information on serum levels.

Conclusion

In patients with HFS, serum Ca, P, and Mg concentration was statistically significantly lower when compared to healthy volunteers, however, there was no statistically significant difference in Fe concentration. These results show us the role of HFS in the pathogenesis of these four trace elements and the importance of its location in etiology. Our study is important in that trace elements are easily accessible and can provide information about the entire system metabolism. We think that the changes in the concentration of trace elements in HFS may initiate mechanisms that can cause spasm due to demyelinization. However, there is a need for more extensive studies to be conducted in this regard.

Aknowlegement

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Conflicts of interest

There are no conflicts of interest.

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