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Ionized calcium levels in stroke patients and its' relation with hemiplegic upper limb pain

Fatih Tok (*), Birol Balaban (**), Evren Yaşar (***), İsmail Safaz (***), Bilge Yılmaz (***), Rıdvan Alaca (***)

ÖZET

İnmeli Hastalarda İyonize Kalsiyum Seviyeleri ve Bunun Hemiplejik Üst Ekstemite Ağrısı ile İlişkisi

AMAÇ: Bu çalışmanın amacı inme sonrası hemipleji gelişen hastalarda hemiplejik taraf üst ekstremitesindeki kemik mineral yoğunluğu ve iyonize kalsiyum değişimleri ile ağrı arasındaki ilişkiyi incelemektir.
MATERYAL VE METOT: Çalışmaya sol hemisferi dominant olan 24 inmeli hasta çalışmaya alındı. Bütün hastalarda spontan veya uyarılmış önkol ağrısı mevcut idi. Hastaların aynı anda sağ ve sol kollarından ayrı ayrı kan alınarak sağ ve sol kol serum iyonize kalsiyum düzeyleri incelendi. Ayrıca DXA kullanırak hastaların sağ ve sol radius kemik mineral yoğunlukları incelendi. Bunun yanında hastaların hemiplejik ekstremitede ağrı VAS ile değerlendirildi.
BULGULAR: Hastaların 12'si erkek, 12'si erkek idi. Hastaların yaş ortalaması 54.33±14.21 yıl idi. Sol hemiplejiklerin hemiplejik taraflarındaki iyonize kalsiyum seviyesi sağ hemiplejiklerin hemiplejik taraf iyionize kalsiyum düzeylerinden anlamlı şekilde düşük idi($p<0.05$). Ağrı ve iyonize kalsiyum düzeyleri arasında korelasyon saptanmaz iken, ağrı düzeyleri ile kemik mineral yoğunluğu arasında negatif korelasyon izlendi.
SONUÇ: Aktif kalsiyum düzeylerindeki değişikler nöromukuler bozuklukların ortaya çıkmasına neden olabilir. Hemiplejik önkol ağrısındaki nöropatik özellikler düşük kalsiyum düzeylerine bağlı olarak kemik mineral yoğunluğunda azalmanın ağrıyı arttırabileceğini akla getirmektedir.

Anahtar Kelimeler: İnme, kalsiyum, ağrı, kemik mineral yoğunluğu

SUMMARY

OBJECTIVE: Our aim is to compare the ionized calcium levels between hemiplegic and normal upper limb and to investigate the relationship between forearm pain and ionized calcium levels.
MATERIAL AND METHODS
24 stroke patients were included in this study. All of them have spontaneous or evoked forearm pain. Ionized serum calcium levels were analysed in both arms by taking blood from both arms at the same time. Additionally, bone minaral density of both radius were detected. Forearm pains of patients were evaluated with VAS.
RESULTS
12 patients were men and others were women. Mean age was 54.33±14.21 years. Serum ionized calcium levels in the hemiplegic side of left hemiplegic patients were significantly less than the levels in right hemiplegic patients. While no correlation was detected between pain and serum ionized calcium levels, negative correlation was detected between radius bone mineral density values and pain levels.
CONCLUSION
Existence of neuromuscular disorders would be possible when there are changes in amount of active form of calcium. Neuropathic features of hemiplegic forearm pain suggest that decreased calcium levels may increase the intensity of pain which is related to bone mineral loss.

Key words: *Stroke, calcium, pain, bone mineral density*

* Iskenderun Marine Regiment Medical Center, Iskenderun, Hatay,
** Turkey European University of Lefke, Faculty of Health Science, Lefke, Cyprus
*** Gulhane Military Medical Academy, Department of Physical Medicine and Rehabilitation, Turkish Armed Forces Rehabilitation Center, Bilkent, Ankara, Turkey

Ayrı Basım İsteği: Fatih Tok
Iskenderun Marine Regiment Medical Center, Iskenderun, Hatay,
e-mail: drfatihtok@gmail.com

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Introduction

Upper limb pain is quite common in hemiplegic patients. This pain usually occurs around the shoulders (1). On the other hand, forearm pains are not uncommon in stroke patients in rehabilitation clinics. Existence of sudomotor changes and allodinia in these patients complicates the diagnosis which is thought to be shoulder-hand syndrome. Spontan or evoked pains accompanying with the sensory disorder related to cerebral lesion can be explained in the favour of post-stroke central pain (2). Furthermore, shoulder hand syndrome is accepted as a neuropatic pain (3). It is difficult to reveal differential diagnose in post-stroke pain and to detect whether the disorder exists from peripheric or central origin , because many pain etiologies can overlap and become confused in patients with stroke.

Observation of osteopenia in hand and wrist graphs may indicate that this pain is associated with bone mineral loss because of immobilization (4). Although paresis and immobilization are important risk factors for osteopenia, pathogenesis of bone mineral loss has not been clearly understood. However, loss of muscle strength and disorders of circulation in paretic extremity, and aging were accepted as leading factors for osteoporosis (5-10).

In recent years, serious researchs about the relation between neuropatic pain and intracellular calcium and calcium chanels have taken place in literature (11). Calcium is an important mineral that plays a critical role in many metabolic processes such as bone metabolism and neuron exitability regulation. Calcium deficiency in itself can lead to carpal symptoms (12).

Calcium may have a role in the pathogenesis of forearm pain in hemiplegic patients. However there is no research about the relationship between forearm pain at paretic side in patients with stroke and serum calcium levels in the literature. We hypothesized that if there is a relationship between pain and serum calcium levels, we can detect it by comparing the serum ionized calcium levels between normal and the hemiplegic arm. The aim of this study is to compare the ionized calcium levels between hemiplegic and normal upper limb and to search the relationship between forearm pain and ionized calcium levels.

Materıal and Methods

24 patients in our Brain Injury Rehabilitation Service were included in this study. All of them have spontaneous or evoked (with pressure and cold stimulus) forearm pain (hyperalgesia and hyperpathia). Dominant hemisphere were left in all pati-

ents and none of them had cooperation difficulty. All patients with Brunnstrom stage 2 and 3 did not have isolated movement in paretic upper limbs in this study. Patients younger than 18 years old; cases with subarachnoid hemorage or rupture of aneurysm, cerebellar or bihemispheric lesions, previous stroke history, any kind of disability before stroke; subjects using medications that effect bone mineral density (D vitamin, biphosphonate, calcitonin, corticosteroit, estrogen, calcium e.g.), having diseases that effect bone mineral density (rheumatoid artritis, chronic renal failure, systemic bone disease, early ooferectomia e.g.), aphasia and history of fracture were exluded from this study. Also, patients who have limitations in shoulder range of motions; shoulder subluxations; edema, abnormal sudomotor activity or allodinia in wrist or forearm, and spotted osteoporosis in X-ray graph of hands were excluded from this study.

Detailed histories were received and physical examinations were done. Duration of illness and stroke etiology according to computerized tomography or magnetic resonance imaging were noted. Ionized serum calcium levels were analysed in both arms by taking blood from both arms at the same time. It was performed for each patient in the morning after a 12 hours overnight fast. Additionally, bone mineral density (BMD) of both radius were detected by using Dual Energy X-ray Absorptiometry (DXA). Forearm pains of patients were evaluated with Visual Analog Scale (VAS) (0-10 cm). Functional upper extremity motor levels of patients were evaluated with Brunnstrom motor staging.

SPSS 13.0 was used for statistical analysis. While Mann Whitney U Test was used for comparing, Spearman test was used for correlation analysis. P<0.05 was accepted for significance.

Table 1: Demographics of patients.

Age (year)	54.33 ± 14.21
Time since stroke (week)	23.83 ± 16.75
Patients with right hemiplegia (n)	14
Patients with left hemiplegia (n)	10
Patients with ischemic stroke(n)	20
Patients with haemoragic stroke (n)	4

Results

12 patients were men and the others were women. Mean age was 54.33 ± 14.21 years. Demographics of patients are shown in Table 1. Pain levels evaluated with VAS in left hemiplegic patients were significantly higher than pain levels in right hemiplegic patients (p<0.05) (Table 2). While serum ionized calcium levels in the hemiplegic arm were higher than normal side in right hemiplegic patients, serum ionized calcium levels in hemiplegic arm were less than normal side in left hemiplegic patients. But these differences were not statistically significant. On the other hand, serum ionized calcium levels in the hemiplegic side of left hemiplegic patients were significantly less than the levels in right hemiplegic patients (p<0.05) (Table 2).

Radius BMD values in hemiplegic upper extremity of all patients were less than the values of the opposite extremity. But this decrease was statistically significant in only left hemiplegic patients (p<0.05) (Tablo 2).

Table 2: BMD of right and left radius, and serum ionized calcium levels of right and left arm.

	Paretic side	N	Mean
Right radius BMD	Right	14	,33 gr/cm^2
	Left	10	,31 gr/cm^2
Left radius BMD	Right	14	,35 gr/cm^2
	Left	10	,29 gr/cm^2
Serum ionized calcium level of right arm	Right	14	4,95 mg/dl
	Left	10	4,84 mg/dl
Serum ionized calcium level of left arm	Right	14	4,92 mg/dl
	Left	10	4,42 mg/dl
Pain (VAS) (cm)	Right	14	1.71
	Left	10	4.70

BMD:Bone Mineral Density

While no correlation was detected between pain and serum ionized calcium levels, negative correlation was detected between radius bone mineral density values and pain levels (r = -0,529 for the right side; r = - 0,684 for the left side; p<0.05). There was no correlation between radius BMD values and serum ionized calcium levels in hemiplegic upper extremities of all cases.

Discussion

Our results are consistent with the literature about post-stroke central pain that left hemiplegic patients suffered more intense pain than right hemiplegic patients (2). Increased serum ionized calcium values is expected in patients with stroke because of immobilization and increased bone resorbsition (13). However, in these studies there is no information about the extremity from which blood example was taken for analysis.

Although the comparıson of serum ionized calcium levels between paretic and normal side were not statistically significant, serum ionized calcium levels in hemiplegic arm of right hemiplegic patients were higher than normal side as aspected. However, serum ionized calcium levels of hemiplegic side in left hemiplegic patients were less than normal side.

Besides, significant decrease was observed in BMD values of paretic arm in left hemiplegic patients. It is a fact that decrease in BMD in opposite side may be more than dominant extremity. We have also observed a meaningful resorption especially in left hemiplegic patients. However, finding of decreases in serum ionized calcium levels of hemiplegic side in left hemiplegic patients was interesting. This reduction was significant in comparison with right hemiplegic patients. Observation of this result in left hemiplegic patients whose pain levels were higher in forearm supports the hypothesis that pain has a relationship with serum ionized calcium levels.

It is not an expected situation that there would be a difference in serum ionized calcium levels when the blood is taken in the same room temperature, same conditions and at the same time (12). Ionized calcium is an active form in metabolic cycle of calcium. The decrease in ionized calcium values in the extracellular fluid suggests the increase in the rate of

binding protein or influx of ionized calcium to intracellular fluid (12). Increase in the rate of binding protein in one side of the body isn't physiological in normal metabolic process and bone resorption. The later possibility that is influx of calcium to intracellular fluid is a more logical theory which supports our hypothesis.

Calcium has critical roles in bone formation, hemostasis, preservation of cell membrane integrity and permeability, muscle contraction, nerve stimulation, secondary messaging in many hormonal activities. Thus, existence of neuromuscular disorders would be possible when there are changes in amount of active form of calcium (12). Increase in intracellular calcium is considered to cause membrane depolarization, phosphorilation of membrane proteins or activation of intracellular enzymes such as phospholipase A2. In particular, ionoforesis which depends on activation of voltage-dependent channels is reported to be important in nociceptive process (11). Besides this, it was reported that increase in intracellular calcium concentration plays an important role in the development of apoptosis or necrosis after central nervous system injury such as stroke. (14). These informations support our hypothesis about the relationship between pain and calcium.

Correlation between bone mineral density and pain level suggests the activation of local nosiceptive process. The mechanism of pain related to osteoporosis has not been thoroughly understood yet. But, it was claimed that chemical agents of local inflammation might cause irritation of nociceptors around periost and joints (15). Meanwhile, it has been claimed that calcitonin decreases the pain due to osteoporosis by effecting the movement of ionic calcium on neuronal membranes (16).

Although a positive relationship was expected between calcium and resorption of bone, it was not detected. This finding can be interpreted as impairment of calcium metabolism in these patients. Neuropathic features of hemiplegic forearm pain suggest that decreased calcium levels may increase the intensity of pain which is related to bone mineral loss.

Main limitation of this study may be the lacking of other biochemical markers of bone cycle. However, we examined ionized calcium as the main factor in this study in which we set off from the assumption that ionized calcium was related with pain and got interesting results.

In conclusion, existence of neuromuscular disorders would be possible when there are changes in amount of active form of calcium. Neuropathic features of hemiplegic forearm pain suggest that decreased calcium levels may increase the intensity of pain which is related to bone mineral loss. Studies with more patients would enlighten the relationhip between pain in paretic arm and calcium in patients with stroke in the future.

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