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

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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 allodynia 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 peripheral 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 parietic 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 channels 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 excitability regulation. Calcium deficiency in itself can lead to carpal tunnel syndrome (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.

Material 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 patients.
ents and none of them had cooperation difficulty. All patients with Brunstrom stage 2 and 3 did not have isolated movement in parietal upper limbs in this study. Patients younger than 18 years old; cases with subarachnoid hemorrhage 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, corticosteroid, estrogen, calcium e.g.), having diseases that effect bone mineral density (rheumatoid arthritis, chronic renal failure, systemic bone disease, early osteoporosis e.g.), aphasia and history of fracture were excluded 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 Brunstrom 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.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>54.33 ± 14.21</td>
</tr>
<tr>
<td>Time since stroke (week)</td>
<td>23.83 ± 16.75</td>
</tr>
<tr>
<td>Patients with right hemiplegia (n)</td>
<td>14</td>
</tr>
<tr>
<td>Patients with left hemiplegia (n)</td>
<td>10</td>
</tr>
<tr>
<td>Patients with ischemic stroke(n)</td>
<td>20</td>
</tr>
<tr>
<td>Patients with haemoragic stroke(n)</td>
<td>4</td>
</tr>
</tbody>
</table>

**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.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Paretic side</th>
<th>N</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right radius BMD</td>
<td>Right</td>
<td>14</td>
<td>.33 gr/cm²</td>
</tr>
<tr>
<td>Left radius BMD</td>
<td>Left</td>
<td>10</td>
<td>.31 gr/cm²</td>
</tr>
<tr>
<td>Serum ionized calcium level of right arm</td>
<td>Right</td>
<td>14</td>
<td>4.95 mg/dl</td>
</tr>
<tr>
<td>Serum ionized calcium level of left arm</td>
<td>Left</td>
<td>10</td>
<td>4.84 mg/dl</td>
</tr>
<tr>
<td>Pain (VAS) (cm)</td>
<td>Right</td>
<td>14</td>
<td>1.71</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>10</td>
<td>4.70</td>
</tr>
</tbody>
</table>

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 resorption (13). However, in these studies there is no information about the extremity from which blood example was taken for analysis.

Although the comparison of serum ionized calcium levels between parietal 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, phosphorylation of membrane proteins or activation of intracellular enzymes such as phospholipase A2. In particular, iontophoresis 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 nociceptive 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 relationship between pain in paretic arm and calcium in patients with stroke in the future.

REFERENCES


