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Association of serum calcium levels with clinical severity of acute ischemic stroke

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Abstract

Background: Calcium (Ca) plays an important role in the pathogenesis of ischemic cell damage. Intracellular Ca accumulation leads neuronal damage by triggering the cycle of cytotoxic events, however the relationship of serum Ca levels and the pathways involved in ischemic injury is unclear. To investigate the effect of serum Ca on clinical features of ischemic stroke; the association of serum Ca levels measured in the first 24 hours with the severity of clinical symptoms on admission and short-term prognosis is evaluated.

Materials and methods: 158 consecutive patients who admitted to the hospital with ischemic stroke in the first 24 hours after the onset of symptoms were enrolled to the study. Serum total Ca levels, National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) scores on admission and mRS scores at discharge were recorded. Patients were classified according to serum total Ca levels into three groups and compared in terms of stroke risk factors, etiology, severity of clinical symptoms on admission and short term prognosis.

Results: A total of 158 patients with acute ischemic stroke including 84 women and 74 men were enrolled in the study prospectively. NIHSS scores were higher in the group1 which consist of lower Ca levels compared with others ($p < 0,05$, $p < 0,001$ respectively), and they were found to be higher in group 2 than group 3 ($p = 0.029$). mRS scores at discharge showed no differences between groups. Except for coronary artery disease was more common in group 2, no statistically significant differences were determined in terms of stroke risk factors and etiology of stroke.

Conclusions: The results of our study reveal that lower Ca levels may be associated with more severe clinical symptoms on admission in acute stroke patients.

Key words: Ischemic stroke; serum calcium levels; clinical outcome; clinical severity; prognosis.

Introduction

Calcium (Ca) plays an important role in the pathogenesis of ischemic cell damage. Intracellular Ca accumulation lead to neuronal damage by triggering the cycle of cytotoxic events. Although the relationship of serum Ca levels and the pathways involved in cell death in acute cerebral ischemia remains unclear; clinical studies suggest that serum Ca levels may be associated with severity of clinical symptoms, prognosis and infarct volume (9, 10, 17, 18). In this study, we evaluated the clinical and prognostic significance of serum Ca levels obtained within 24 hours of stroke onset.

Materials and methods

158 consecutive patients who were admitted to the hospital within 24 hours of stroke onset were enrolled in the study. All the patients were over the age of 18 and ischemic stroke was diagnosed with computed brain tomography or diffusion magnetic resonance imaging. Risk factors for cerebrovascular disease as hypertension, hypercholesterolemia, diabetes mellitus, coronary artery disease, atrial fibrillation, valvular heart disease, prior transient ischemic attacks or stroke were recorded. Systolic blood pressure 140 mmHg or higher, diastolic blood pressure 90 mmHg or higher or both, was diagnosed as hypertension. Cholesterol levels higher than 200 mg/dl were considered to be hypercholesterolemia. The diagnosis of diabetes mellitus was confirmed with the use of antidiabetic agents prior to stroke or fasting blood glucose higher than 120 mg/dl. Hematological and biochemical laboratory tests, electrocardiography, echocardiography and carotid-vertebral artery color Doppler ultrasonography of patients were performed. Etiological classification of patients was done according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (5). National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS) scores on admission and mRS scores at discharge were recorded. Patients were divided into three groups according to their

serum total calcium levels and stroke risk factors, etiology, clinical symptoms on admission and short-term prognosis were compared within groups.

Statistical analysis

Data analysis was performed in SPSS for Windows 11.5 packet program. Continuous variables were shown as mean ± standard deviation, ordinal variables were shown as the median (minimum-maximum) and nominal variables were shown as the number of cases and percentage. Calcium levels were divided into three groups by using weighted average. As the significance of the differences in terms of mean values was assessed by one-way variance analysis, the significance of the differences of the median values was analyzed by Kruskal Wallis test. In case of the result of Kruskal Wallis test is found to be significant, non-parametric multiple comparison test was used in order to determine the group or groups that caused significant difference. Nominal variables were evaluated with Pearson chi-square or Fisher's exact chi-square test results. The results were considered statistically significant for $p < 0.05$.

Results

A total of 158 patients with acute ischemic stroke including 84 women and 74 men were enrolled in the study. The mean duration of the patients' hospital stay was 8.96 (3-42) days. The patients were divided into three groups according to serum total Ca levels. Patients with Ca ≤ 4,3 mEq/l were included in group 1, Ca levels between 4,4 and 4,7 mEq/l were included in group 2, and Ca ≥ 4,8 mEq/l were included in group 3. (Reference laboratory value of serum total Ca is between 4,3 and 5,2 mEq/l). In group 1, there were more women patients than group 2 and 3. Coronary artery disease was more common in group 2 than group 3. No statistically significant difference was determined in terms of other stroke risk factors between the groups. Table 1 displays the demographic characteristics of patients and risk factors for stroke according to calcium levels. No statistically significant difference was determined in terms of etiology of stroke. NIHSS scores on admission were higher in group1 than group 2 and 3 ($p < 0,05$, $p < 0,001$ respectively), and they were found to be higher in group 2 than group 3 ($p = 0,029$). While the mRS scores on admission were higher in group 1 than group 2 and 3, the mRS scores at discharge showed no difference between groups. Etiology of stroke, NIHSS and mRS scores on admission, and the mRS scores at discharge by Ca levels are shown in table 2.

Discussion

There are a few clinical studies which looked at the prognostic significance of serum Ca levels in acute stroke patients (1, 3, 4). Serum Ca values were found to decrease in patients with cerebral infarction and lower total serum Ca levels were detected in

Table 1

Demographic characteristics of patients and risk factors for stroke according to calcium levels

	Group I (n = 49) Ca ≤ 4,3 mEq/l	Group II (n = 59) Ca 4,4-4,7 mEq/l	Group III (n = 50) Ca ≥ 4,8 mEq/l	p
Age	68,3 ± 11,9	67,1 ± 10,8	65,4 ± 10,0	0,415[a]
Woman sex	34 (%69,4)[c,d]	28 (%47,5)[c]	22 (%44,0)[d]	0,022[b]
Hypertension	31 (%63,3)	46 (%78,0)	31 (%62,0)	0,133[b]
Diabetes mellitus	13 (%26,5)	19 (%32,2)	12 (%24,0)	0,616[b]
Hypercholesterolemia	21 (%42,9)	25 (%42,4)	21 (%42,0)	0,996[b]
Prior TIA*/stroke	16 (%32,7)	19 (%32,2)	14 (%28,0)	0,855[b]
Coronary artery disease	13 (%26,5)	26 (%44,1)[e]	12 (%24,0)[e]	0,048[b]
Valvular heart disease	9 (%18,4)	5 (%8,5)	2 (%4,0)	0,052[b]
Atrial fibrillation	9 (%18,4)	12 (%20,3)	10 (%20,0)	0,384[b]

[a] One-way variance analysis.
[b] Pearson Chi-Square test.
[c] Difference between Group I and Group II is statistically significant (p = 0,022).
[d] Difference between Group I and Group III is statistically significant (p = 0,011).
[e] Difference between Group II and Group III is statistically significant (p = 0,028).
* Transient ischemic attack.

Table 2

Etiology of stroke, admission NIHSS and mRS scores and discharge mRS scores according to calcium levels

	Group I (n = 49) Ca ≤ 4,3 mEq/l	Group II (n = 59) Ca 4,4-4,7 mEq/l	Group III (n = 50) Ca ≥ 4,8 mEq/l	p
Etiology				
Large vessel disease	14 (%28,6)	13 (%22,0)	17 (%34,0)	0,378[a]
Small vessel disease	6 (%12,2)	17 (%28,8)	11 (%22,0)	0,113[a]
Cardioembolic	21 (%42,9)	22 (%37,3)	17 (%34,0)	0,656[a]
Other	–	–	1 (%2,0)	–
Unknown	8 (%16,3)	7 (%11,9)	4 (%8,0)	0,444[a]
Admission NIHSS	7 (1-17)[c,d]	5 (2-17)[c,e]	3 (1-16)[d,e]	< 0.001[b]
Admission mRS	5 (1-6)[c,d]	3 (1-6)[c]	3 (1-6)[d]	< 0.001[b]
Discharge mRS	3 (0-7)	3 (1-7)	3 (0-6)	0.144[b]

[a] Pearson Chi-Square test
[b] Kruskal Wallis test.
[c] Difference between Group I and Group II is statistically significant (p < 0,05).
[d] Difference between Group I and Group III is statistically significant (p < 0,001).
[e] Difference between Group II and Group III is statistically significant (p = 0,029).

patients who died during hospitalization compared with survivors (1). It is also reported that higher total serum Ca values detected on admission in acute ischemic stroke patients were associated with smaller cerebral infarct volumes (2). Ovbiagele and colleagues found that higher total serum Ca values measured in the first 24 hours were associated with lesser severity of the stroke and better functional prognosis at discharge (3). In their later study they also reported that total serum Ca levels in a very early period of ischemic stroke (< 4.5 hour) did not have prognostic significance, but higher serum Ca levels 72-96 hours after stroke were associated with better clinical outcomes in the third month (4).

The results of our study reveal that lower total serum Ca values measured in the first 24 hours of ischemic stroke are associated with more severe clinical findings. But we couldn't define any association between calcium levels and short-term prognosis. Although small vessel disease is found to be less often in lower Ca group, we couldn't define any statistically significant differences between the groups in terms of stroke etiology.

In cell death due to central nervous system ischemia, it is known that there are many mechanisms take place as excitotoxicity, oxidative stress, apoptosis and necrotic cell death. Each of these mechanisms requires cation entry to neural cells. Uncontrolled entry of calcium into cells triggers necrotic and apoptotic cell death (6). Until recently, it has been accepted that calcium influx into the cell via NMDA receptors was the main pathway for delayed cell death and excitotoxicity associated with ischemia (6, 7). However it has been demonstrated that other pathways such as transient receptor potential (TRP) channels and non-selective cation (NC) channels which cause an ionic imbalance may be up-regulated during ischemia and play a role in Ca-mediated neuronal death (6, 8). Restoring extracellular Ca following a period of lower Ca concentrations is known to cause a paradoxical increase in intracellular Ca levels. It is suggested that TRP channels were likely to contribute to both Ca paradox and delayed neuronal death following ischemic stroke (6, 7). Entry of Ca into cells through NMDA receptors and voltage-dependent Ca channels potentially reduces the extracellular Ca and this reduction causes disinhibition of the Ca-sensing non-selective channel current (I_{csNSC}) and to further membrane depolarization and more Ca influx (7). On the other hand, as the extracellular pH decreases during ischemia, the acid-sensing ion channels (ASIC) are activated. ASIC activation is promoted by stretching of membrane, release of arachidonic acid, production of lactate or decrease in extracellular Ca concentration in conditions that occur in neurons subjected to ischemia and leads to Ca influx (6, 7, 9). Moreover, it is suggested that subtle increase in extracellular Ca may effects intracellular second messengers by Ca-sensing receptors (CaR) and may start antiapopitotic pathway. With the demonstration of CaR protein expression, it is also suggested that Ca is not only an intracellular second messenger as regarded before, but also may act as an external

ligand and the extracellular Ca may be an important first messenger (10-12).

Besides the hypothesis that serum Ca level exerts a primary effect on ischemic stroke, serum Ca decrease may reflects a response to the presence of tissue ischemia. Cerebral ischemia causes at least temporary depletion of extracellular Ca because of Ca influx and intracellular Ca accumulation (13, 14). But it is not clear whether the magnitude and temporal course of this decrease is sufficient to account for the lower Ca levels observed in patients with infarction (2-4).

In experimental studies a significant decrease in histological damage due to ischemia is observed in rats treated with Ca infusion (15), and a reduction in stroke mortality is defined after Ca supplementation (16). Epidemiological studies evaluating the association between calcium and stroke risk factors and stroke incidence were done as well as experimental studies. High dietary intake of Ca has been associated with reduced risk of stroke (17-19). In addition to hypotensive effect of Ca (20-22), it is also suggested that Ca reduces platelet aggregation (23) and lowers plasma cholesterol levels (24, 25). Interestingly, the role of serum Ca is not only limited to ischemic stroke as a clinical prognostic factor. It has been reported that hypocalcaemia is associated with more severe disease and high mortality in many diseases, particularly in critical illnesses (26, 27).

Our study may have limitation, because we measured total Ca levels rather than ionized or albumin-corrected serum Ca levels. A previous study that compared total Ca, ionized Ca and albumin-corrected Ca; only the total serum Ca level was shown to be of prognostic value for mortality in stroke patients (1). Furthermore prognostic significance of albumin-corrected Ca hadn't been demonstrated in another study (4).

The results of our study reveal that lower serum Ca levels may be associated with more severe clinical findings at onset in stroke patients. Serum Ca levels may reflect the severity of ischemic injury and may be a potential therapeutic target for improving stroke outcome.

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