Low Serum Calcium and Magnesium Levels and Rupture of Intracranial Aneurysms

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Background and Purpose—Both low serum calcium and magnesium levels have been associated with the extent of bleeding in patients with intracerebral hemorrhage, suggesting hypocalcemia- and hypomagnesemia-induced coagulopathy as a possible underlying mechanism. We hypothesized that serum albumin-corrected total calcium and magnesium levels are associated with ruptured intracranial aneurysms.

Methods—The medical records of 4701 patients, including 1201 prospective patients, diagnosed at the Brigham and Women's Hospital and Massachusetts General Hospital between 1990 and 2016 were reviewed and analyzed. One thousand two hundred seventy-five patients had available serum calcium, magnesium, and albumin values within 1 day of diagnosis. Individuals were divided into cases with ruptured aneurysms and controls with unruptured aneurysms. Univariable and multivariable logistic regression analyses were performed to determine the association between serum albumin-corrected total calcium and magnesium levels and ruptured aneurysms.

Results—In multivariable analysis, both albumin-corrected calcium (odds ratio, 0.33; 95% confidence interval, 0.27–0.40) and magnesium (odds ratio, 0.40; 95% confidence interval, 0.28–0.55) were significantly and inversely associated with ruptured intracranial aneurysms.

Conclusions—In this large case–control study, hypocalcemia and hypomagnesemia at diagnosis were significantly associated with ruptured aneurysms. Impaired hemostasis caused by hypocalcemia and hypomagnesemia may explain this association. **(*Stroke*. 2018;49:1747-1750. DOI: 10.1161/STROKEAHA.118.020963.)**

Key Words: aneurysm ■ calcium ■ magnesium ■ rupture ■ subarachnoid hemorrhage

Recently, both hypocalcemia and hypomagnesemia have been significantly associated with extent of bleeding in patients with intracerebral hemorrhage.[1–3] Because both calcium and magnesium are involved in platelet function and the coagulation cascade, impaired hemostasis caused by hypocalcemia and hypomagnesemia may explain this association.[2,4–6] In addition, hypomagnesemia has been associated with severity of aneurysmal subarachnoid hemorrhage (aSAH) and related complications such as delayed cerebral ischemia,[7] although conflicting results have been reported.[8] However, studies investigating this association in the context of intracranial aneurysm rupture risk are lacking. Here, we present a large case–control study investigating the association between albumin-corrected total calcium and magnesium values at admission and the risk of aSAH.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request. Four thousand seven hundred one patients who were diagnosed with an intracranial aneurysm between 1990 and 2016 at the Brigham and Women's Hospital and Massachusetts General Hospital were identified with both machine-learning algorithms and manual medical chart review. This study was approved by our institutional review board and considered minimal risk. Patient consent was, therefore, waived by the board. Patients were identified both prospectively on clinical presentation (2007–2016) and retrospectively using natural language processing in conjunction with the Partners Healthcare Research Patients Data Registry.[9] Detailed methods are provided in the online-only Data Supplement. Inclusion criteria were limited to patients with available serum total calcium, magnesium, and albumin measurements within 1 day of diagnosis, leading to a final total number of 1275 eligible patients.

Univariable and multivariable logistic regression models were implemented to test for effects of serum total calcium, albumin, and magnesium. All statistical analyses were performed using the Stata statistical software package (version 14; StataCorp, College Station, TX).

Results

Patient demographics and characteristics, as well as laboratory values, are shown in Tables I and II in the online-only Data

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Supplement. A total of 1275 patients with 1704 aneurysms were included, of which 900 (70.6%) were ruptured. Patients with hypocalcemia (albumin-corrected) were significantly more frequently diagnosed with ruptured aneurysms and also had lower magnesium values. When albumin-corrected calcium and magnesium values from within 1 year before rupture were compared with values within 1 day after rupture in the same patient, there were no significant differences for both albumin-corrected calcium (P=0.13) and magnesium levels (0.99), indicating that lower calcium and magnesium levels after rupture were not primarily because of the rupture itself. Given the association of calcium and the anticoagulation pathway, we examined a subgroup of patients without oral anticoagulation therapy. In this subgroup, international normalized ratio values were higher in patients with hypocalcemia (international normalized ratio, 1.30; 95% confidence interval [CI], 1.17–1.43) compared with patients without hypocalcemia (international normalized ratio, 1.15; 95% CI, 1.00–1.30), but the difference was not statistically significant.

The Table shows the results of the univariable and multivariable analyses. In multivariable analysis, younger age, black race, Asian race, current alcohol use, and current tobacco use were significantly associated with aSAH. In contrast, coronary artery disease (odds ratio, 0.51; 95% CI, 0.29–0.91), higher albumin-corrected total calcium (odds ratio, 0.33; 95% CI, 0.27–0.40), and higher magnesium (odds ratio, 0.50; 95% CI, 0.34–0.75) were significantly associated with a lower rupture risk. The direction and significance of all coefficients remained similar in the sensitivity analyses using complete cases only (Table III in the online-only Data Supplement). The Figure shows the proportion of ruptured aneurysms stratified according to serum albumin-corrected total calcium levels and magnesium levels within 1 day of diagnosis.

Discussion

Inoue et al[3] demonstrated a relationship between low admission serum calcium levels and larger hematoma volume among patients with acute intracerebral hemorrhage. This finding was confirmed in another cohort study where hypocalcemia was associated with larger baseline intracerebral hemorrhage volumes and hematoma expansion.[1] The authors hypothesized that low levels of calcium may lead to hematoma enlargement because of calcium's role in platelet function and the coagulation cascade.[1] Because oral anticoagulation therapy may affect coagulation physiology, we examined patients who were not on oral anticoagulants at the time of diagnosis.[1] In this subgroup, patients with hypocalcemia (albumin-corrected calcium <8.4 mg/dL) had higher international normalized ratio values than nonhypocalcemic patients. Although the difference was not significant, the trend suggests that hypocalcemia-induced subtle alterations of the coagulation pathway may predispose aneurysms to increased risk of rupture. Another possible mechanism by which hypocalcemia could lead to aSAH is vasoconstriction and subsequent elevation of blood pressure by affecting vascular reactivity.[10–13] However, hypertension was not significantly more common among hypocalcemic patients in our cohort. This is consistent with the study by Morotti et al[1] that also failed to show an association between calcium values and hypertension.

Although administration of magnesium in patients with acute stroke did not demonstrate functional outcome benefits in a randomized controlled trial,[14] Liotta et al[2] recently found

Table. Univariable and Multivariable Logistic Regression for Rupture Status Including Serum Laboratory Values Within 1 Day of Diagnosis (n=1275)

	Univariable*		Multivariable*	
Characteristics	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Female	1.02 (0.78–1.34)	0.87	1.25 (0.92–1.71)	0.16
Black race (vs white race)	1.34 (0.85–2.11)	0.21	1.91 (1.13–3.23)	0.02
Hispanic race (vs white race)	0.87 (0.54–1.38)	0.55	0.85 (0.50–1.45)	0.54
Asian race (vs white race)	2.01 (0.88–4.62)	0.10	2.65 (1.04–6.74)	0.04
Other/unknown race (vs white race)	1.52 (0.88–2.61)	0.13	1.75 (0.95–3.22)	0.07
Age at diagnosis	0.97 (0.96–0.98)	<0.01	0.98 (0.97–0.99)	<0.01
Coronary artery disease	0.40 (0.25–0.65)	<0.01	0.51 (0.29–0.91)	0.02
Myocardial infarction	0.47 (0.28–0.79)	0.01	0.69 (0.37–1.27)	0.24
Hypertension	0.64 (0.50–0.82)	<0.01	0.87 (0.65–1.16)	0.35
Atrial fibrillation	0.44 (0.26–0.75)	<0.01	0.69 (0.37–1.28)	0.24
No. of aneurysms	1.04 (0.89–1.23)	0.50	1.02 (0.85–1.23)	0.80
Family history aneurysms	0.90 (0.62–1.30)	0.57	0.85 (0.55–1.30)	0.44
Current tobacco use	2.31 (1.75–3.04)	<0.01	2.13 (1.55–2.92)	<0.01
Current alcohol use	1.70 (1.32–2.19)	<0.01	1.66 (1.23–2.23)	<0.01
Albumin-corrected total calcium, mg/dL	0.34 (0.28–0.41)	<0.01	0.33 (0.27–0.40)	<0.01
Magnesium, mg/dL	0.40 (0.28–0.55)	<0.01	0.50 (0.34–0.75)	<0.01

Multiple imputation (40 imputations) with chained equations was used for missing data.

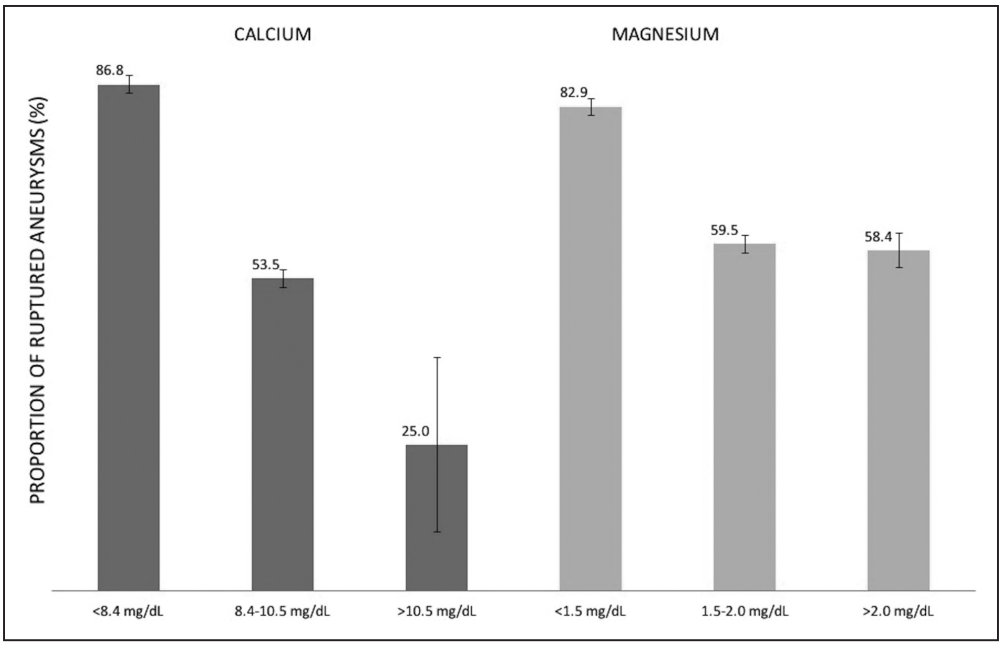

Figure. Percentage of ruptured aneurysms stratified according to serum albumin-corrected total calcium and magnesium levels at diagnosis.

in an observational cohort study that lower magnesium levels at admission were associated with larger intracerebral hemorrhage volumes, hematoma growth, and worse functional outcome. Interestingly, it has been shown that magnesium also plays a crucial role in the coagulation pathway, platelet activation, and hemostasis, possibly supporting the hypothesis that hypomagnesemia-induced coagulopathy may have implications in the pathophysiology of intracranial aneurysm rupture. Sekiya et al[6] showed that magnesium ions significantly augment the biological activities of factor IX. However, the question remains whether hypomagnesemia is associated with the cause or the effect of aSAH.[7] Another possible mechanism for hypomagnesemia after acute stroke or SAH is acidosis-associated increase in intracellular brain magnesium levels, with a subsequent decrease in serum magnesium levels.[7,15] Taken together, our findings suggest that hypocalcemia- and hypomagnesemia-related impairment of the coagulation cascade could explain the increased association with rupture of intracranial aneurysms. However, these mechanistic links need to be further explored in future studies.

Some of the major strengths of our study are the high-quality standardized database, the large sample size, and the presence of a large control group. The main limitations include the retrospective design for a portion of the patients, the lack of prerupture measurements in the majority of patients, and the lack of ionized calcium values. However, we have albumin values to account for the effects of albumin on serum calcium. In some cases of aSAH, history of tobacco and alcohol consumption was obtained from relatives of patients, possibly leading to information bias. Finally, although there was no significant difference in the albumin-corrected calcium levels before and after rupture, there is a trend toward hypocalcemia after rupture. It is possible that the hypocalcemia may be secondary to the hemorrhage, and the lack of statistical significance may be because of insufficient power.

Summary

Our data showed that hypocalcemia and hypomagnesemia at diagnosis were significantly associated with ruptured aneurysms, which may be explained by impaired hemostasis. Further large prospective trials are needed to confirm our findings.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Supplemental Methods

Patients were identified both prospectively on clinical presentation (2007-2016) and retrospectively using natural language processing (NLP) in conjunction with the Partners Healthcare Research Patients Data Registry (RPDR) which includes 4.2 million patients who have received care from BWH and MGH (1990-2013).[1] With the use of ICD-9 and CPT codes we obtained an initial set of potential aneurysm patients from the RPDR, and we then used NLP to train a classification algorithm which yielded 5,589 patients. 727 of these patients were also seen on clinical presentation from 2007-2013 with prospectively collected data. We included 474 additional patients with prospectively collected data who were seen on clinical presentation from 2013-2016. Then we reviewed the medical records and imaging studies of the 6,063 patients in detail (AC and RD) to ultimately identify 4,701 patients with definite saccular aneurysms. Inclusion criteria were limited to patients with available serum total calcium, magnesium, and albumin measurements within 1 day of diagnosis/rupture, leading to a final total number of 1,275 eligible patients. We recorded the results of the imaging studies and excluded patients with possible infundibula or non-definitive diagnoses of aneurysms, feeding artery aneurysms associated with arteriovenous malformations, fusiform or dissecting aneurysms, and those lacking clinical notes or radiographic images. Patients who received treatment of their aneurysm(s) prior to presentation were excluded from this study and patients who presented with an aneurysmal subarachnoid hemorrhage were categorized as harboring a ruptured aneurysm.

Patient characteristics including age, sex and race, and comorbidities including history of coronary artery disease, hypertension, myocardial infarction, and atrial fibrillation were obtained. A risk factor was assumed to be absent if we found no documentation of its presence. In addition, we included the total number of intracranial aneurysms per patient, family history of aneurysms, INR values obtained at the time of diagnosis for patients with ruptured aneurysms and within a year of diagnosis for unruptured patients, and information on current tobacco and alcohol use. The diagnosis of aSAH was confirmed with a computed tomographic (CT) scan, cerebrospinal fluid analysis, or intraoperatively by a neurosurgeon. Calcium values were corrected for based on the serum albumin values: corrected calcium (mg/dL) = calcium (mg/dL) + 0.02*(4.0-albumin (g/dL)).

Differences in baseline characteristics between the ruptured and unruptured groups were evaluated using *t*-tests for continuous variables and Pearson's chi-square test for categorical variables. Univariable and multivariable logistic regression models were implemented to test for effects of serum total calcium, albumin, and magnesium values. All covariates were included in the multivariable model. Adjusted odds ratios (OR) with 95% confidence intervals (CI's) were calculated, and $p< 0.05$ was considered significant. Missing values were accounted for by using multiple imputation with chained equations and inferential statistics were obtained from 40 imputed datasets. Sensitivity analysis using a subgroup consisting of complete cases only was also performed. To determine changes in magnesium levels and albumin-corrected calcium

levels up to 1 year before and up to 1 day after a rupture within the same patient, a mixed model was used with the patient as the random effects variable. All statistical analyses were performed using the Stata statistical software package (version 14, StataCorp. College Station, TX).

Supplemental Table I. Patient characteristics stratified by hypocalcemia status.

Variables	All N=1,275	Missing	Hypocalcemia <1 day of diagnosis* N= 454	Non-hypocalcemia <1 day of diagnosis N=821	P
Female (%)	922 (72.3)	0	336 (74.0)	586 (71.4)	0.25
Race					0.22
White race (%)	961 (75.4)	0	334 (73.6)	627 (76.4)	
Black race (%)	109 (8.5)	0	33 (7.3)	76 (9.3)	
Hispanic race (%)	86 (6.7)	0	37 (8.1)	49 (6.0)	
Asian race (%)	39 (3.1)	0	16 (3.5)	23 (2.8)	
Other/unknown race (%)	80 (6.3)	0	34 (7.5)	46 (5.6)	
Age at diagnosis (SD)	55.3 (14.2)	0	54.0 (14.1)	56.0 (14.3)	0.01
Coronary artery disease (%)	73 (5.7)	0	29 (6.4)	44 (5.4)	0.46
Myocardial infarction (%)	61 (4.8)	0	20 (4.4)	41 (5.0)	0.63
Hypertension (%)	655 (51.4)	0	221 (48.7)	434 (52.9)	0.15
Atrial fibrillation (%)	59 (4.6)	0	19 (4.2)	40 (4.9)	0.57
Number of aneurysms (SD)	1.34 (0.76)	0	1.37 (0.77)	1.32 (0.76)	0.31
Family history aneurysms (%)	143 (11.2)	0	52 (11.5)	91 (11.1)	0.84
Current tobacco use (%)	443 (35.7)	35	154 (35.0)	289 (36.1)	0.69
Current alcohol use (%)	547 (46.5)	98	180 (44.0)	367 (47.8)	0.22
Ruptured aneurysms (%)	900 (70.6)	0	396 (87.2)	504 (61.4)	<0.01
INR (all patients) (SD)	1.74 (0.81)	1205	1.51 (0.48)	1.89 (0.95)	0.03
INR (patient without oral anticoagulation therapy) (SD) **	1.23 (0.25)	1204	1.30 (0.22)	1.15 (0.26)	0.11
Serum magnesium (<1day) (mg/dL) (SD)	1.74 (0.36)	0	1.68 (0.43)	1.77 (0.30)	<0.01

* Hypocalcemia is defined as an albumin-corrected total serum calcium level less than 8.4 mg/dL

** Among a subgroup of patients without oral anticoagulation therapy (N=1,232)

Supplemental Table II. Patient characteristics stratified by rupture status.

Variables	All N=1,275	Missing	Ruptured N=900	Non-ruptured N=375	P
Female (%)	922 (72.3)	0	270 (72.0)	652 (72.4)	0.87
Race					0.22
White race (%)	961 (75.4)	0	294 (78.4)	667 (74.1)	
Black race (%)	109 (8.5)	0	27 (7.2)	82 (9.1)	
Hispanic race (%)	86 (6.7)	0	29 (7.7)	57 (6.3)	
Asian race (%)	39 (3.1)	0	7 (1.9)	32 (6.9)	
Other/unknown race (%)	80 (6.3)	0	18 (4.8)	62 (3.6)	
Age at diagnosis (SD)	55.3 (14.2)	0	59.8 (14.2)	53.5 (13.8)	<0.01
Coronary artery disease (%)	73 (5.7)	0	36 (9.6)	37 (4.1)	<0.01
Myocardial infarction (%)	61 (4.8)	0	28 (7.5)	33 (3.7)	0.01
Hypertension (%)	655 (51.4)	0	222 (59.2)	433 (48.1)	<0.01
Atrial fibrillation (%)	59 (4.6)	0	28 (7.5)	31 (3.4)	<0.01
Number of aneurysms (SD)	1.34 (0.76)	0	1.32 (0.67)	1.34 (0.80)	0.59
Family history aneurysms (%)	143 (11.2)	0	45 (12.0)	98 (10.9)	0.57
Current tobacco use (%)	443 (35.7)	35	87 (23.3)	356 (41.1)	<0.01
Current alcohol use (%)	547 (46.5)	98	136 (37.4)	411 (50.6)	<0.01
INR (all patients) (SD)	1.74 (0.81)	1205	1.74 (0.81)	1.73 (0.83)	0.98
INR (patient without oral anticoagulation therapy) (SD) **	1.23 (0.25)	1204	1.24 (0.24)	1.22 (0.26)	0.88
Serum corrected calcium (<1 day) (mg/dL) (SD)	8.60 (0.89)	0	9.07 (0.76)	8.40 (0.87)	<0.01
Serum magnesium (<1day) (mg/dL) (SD)	1.74 (0.36)	0	1.82 (0.32)	1.70 (0.37)	<0.01

Supplemental Table III. Univariable and multivariable logistic regression for rupture status including serum laboratory values within 1 day of diagnosis (N=1,167) in complete cases only.

	Univariable*		Multivariable*	
Characteristics	OR (95% CI)	P	OR (95% CI)	P
Female	1.02 (0.78-1.34)	0.87	1.27 (0.92-1.75)	0.15
Black race (vs. white race)	1.33 (0.85-2.11)	0.21	1.94 (1.14-3.32)	0.02
Hispanic race (vs. white race)	0.87 (0.54-1.38)	0.55	0.70 (0.40-1.24)	0.22
Asian race (vs. white race)	2.01 (0.88-4.62)	0.10	2.66 (1.02-6.91)	0.045
Other/unknown race (vs. white race)	1.52 (0.88-2.61)	0.13	2.08 (1.04-4.13)	0.04
Age at diagnosis	0.97 (0.96-0.98)	<0.01	0.98 (0.97-0.99)	<0.01
Coronary artery disease	0.40 (0.25-0.65)	<0.01	0.50 (0.27-0.90)	0.02
Myocardial infarction	0.47 (0.28-0.79)	0.01	0.72 (0.39-1.34)	0.30
Hypertension	0.64 (0.50-0.82)	<0.01	0.93 (0.68-1.26)	0.62
Atrial fibrillation	0.44 (0.26-0.75)	<0.01	0.78 (0.41-1.47)	0.44
Number of aneurysms	1.04 (0.89-1.23)	0.62	1.02 (0.85-1.23)	0.21
Family history aneurysms	0.90 (0.62-1.30)	0.57	0.91 (0.59-1.40)	0.67
Current tobacco use (vs. not current)	2.30 (1.75-3.03)	<0.01	2.20 (1.59-3/03)	<0.01
Current alcohol use (vs. not current)	1.71 (1.33-2.21)	<0.01	1.68 (1.25-2.26)	<0.01
Serum total corrected calcium (mg/dL)	0.34 (0.28-0.41)	<0.01	0.32 (0.26-0.39)	<0.01
Serum magnesium (mg/dL)	0.40 (0.28-0.55)	<0.01	0.52 (0.34-0.78)	<0.01

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