Serum Glucose and Potassium Ratio as Risk Factors for Cerebral Vasospasm after Aneurysmal Subarachnoid Hemorrhage

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Objective: Cerebral vasospasm is associated with poor prognosis in patients with aneurysmal subarachnoid hemorrhage (SAH), and biomarkers for predicting poor prognosis have not yet been established. We attempted to clarify the relationship between serum glucose/potassium ratio and cerebral vasospasm in patients with aneurysmal SAH. *Methods:* We studied 333 of 535 aneurysmal SAH patients treated between 2006 and 2016 (123 males, 210 females; mean age 59.7 years; range 24-93). We retrospectively analyzed the relationship between cerebral vasospasm grade and clinical risk factors, including serum glucose/potassium ratio. *Results:* Postoperative angiography revealed cerebral vasospasm in 112 patients (33.6%). Significant correlations existed between the ischemic complication due to cerebral vasospasm and glucose/potassium ratio ($P < .0001$), glucose ($P = .016$), and potassium ($P = .0017$). Serum glucose/potassium ratio was elevated in the cerebral vasospasm grade dependent manner (Spearman's $r = 0.1207$, $P = .0279$). According to the Glasgow Outcome Scale (GOS) score at discharge, 185 patients (55.5%) had a poor outcome (GOS scores 1-3). Serum glucose/potassium ratio was significantly correlated between poor outcome (GOS scores 1-3) and age ($P < .0001$), serum glucose/potassium ratio ($P < .0001$), glucose ($P < .0001$), potassium ($P = .0004$), white blood cell count ($P = .0012$), and cerebral infarction due to cerebral vasospasm ($P < .0001$). Multivariate logistic regression analyzes showed significant correlations between cerebral infarction due to cerebral vasospasm and serum glucose/potassium ratio ($P = .018$), glucose ($P = .027$), and potassium ($P = .052$). *Conclusions:* Serum glucose/potassium ratio in cases of aneurysmal SAH was significantly associated with cerebral infarction due to cerebral vasospasm and GOS at discharge. Therefore, this factor was useful to predict prognosis in patients with cerebral vasospasm and aneurysmal SAH.

Key Words: Aneurysmal subarachnoid hemorrhage—biomarker—cerebral vasospasm—glucose—potassium

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Abbreviations: ACA, anterior cerebral artery; AcoA, anterior communicating artery; BA, basilar artery; BNP, brain natriuretic peptide; CRP, C-reactive protein; GOS, Glasgow Outcome Scale; H&K, Hunt and Kosnik; ICA, internal carotid artery; MCA, middle cerebral artery; MRIDWI, magnetic resonance imaging diffusion-weighted imaging; NO, nitrous oxide; SAH, subarachnoid hemorrhage; VA, vertebral artery; WBC, white blood cell

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Introduction

Subarachnoid hemorrhage (SAH) due to ruptured cerebral aneurysm is associated with poor prognosis. Its impact on society is significant since many patients have after effect, such as disturbance of consciousness, hemiparesis, and high-order brain dysfunction.[1,2]

Important factors related to prognosis in patients with SAH are mainly initial brain damage and postoperative cerebral vasospasm.[3] Especially in cerebral vasospasm, patients with a good postoperative course often have sudden onset of hemiparesis, aphasia, and disturbance of consciousness despite progression of treatment to date.[4] Therefore, prevention and prediction of cerebral vasospasm are especially important to improve prognosis after SAH.[5]

Various methods of predicting cerebral vasospasm after aneurysmal SAH have been reported, including Fisher grade, age, and biomarkers, such as white blood cell (WBC) count, electrolyte abnormality, and C-reactive protein (CRP).[6-8] However, few reports have studied the relationship between serum glucose/potassium ratio and cerebral vasospasm after aneurysmal SAH.

Previously, we reported the relationship of serum glucose/potassium ratio with aneurysmal SAH and prognosis.[9] In the present study, we analyzed the relationship of serum glucose/potassium ratio and cerebral vasospasm.

Methods

The study is reported based on criteria from the Strengthening the Reporting of Observational Studies in Epidemiology statement and was approved by Chiba Hokusoh Hospital Research Ethics Committee, Chiba, Japan.

Preoperative Examination and Treatment

We investigated serum glucose/potassium ratio and prognosis of aneurysmal SAH 565 patients who underwent surgery at our institution between January 2006 and 2016.[10] Exclusion criteria were patients who refused surgery, postoperative angiography, and diffusion-weighted magnetic resonance imaging (MRIDWI).

All SAH cases were diagnosed by computed tomography on the day of admission. Laboratory data investigated at admission to our hospital included potassium (mEq/l), glucose (mg/dl), WBC (μ/l), and CRP (mg/dl). All patients underwent cerebral angiography to determine the ruptured aneurysm size and location. At our institution, we treated aneurysmal SAH by clipping during the acute stage (<2 days). Perioperative care was performed according to standardized protocol provided by the guidelines for the management of aneurysmal SAH in Japan.[11] All patients underwent angiography on postoperative day 7 to detect the cerebral vasospasm and confirm complete clip ligation. We checked glucose levels 4 times per day and controlled the blood glucose value at 144-180 mg/dl using sliding scale insulin therapy postoperatively.[12]

We retrospectively reviewed data from patients' charts, including admission data, laboratory work-up, imaging data, and follow-up reports.

Outcome Assessment

Cerebral vasospasm (less than 50% of the narrowing vessel diameter in the M1, M2, A1, and P1 portions compared with initial values) and cerebral infarction due to cerebral vasospasm (judged using MRIDWI within day 3-14) were judged by more than two neurosurgeon. We divided cerebral vasospasm into four grades: Grade 0 (no cerebral vasospasm group), 51% to 99% of the narrowing vessel diameter with no symptoms and no complicated cerebral infarction on MRIDWI; Grade 1, <50% of the narrowing vessel diameter with no symptoms and no complicated cerebral infarction on MRIDWI; Grade 2 <50% of the narrowing vessel diameter with appearance of clinical symptoms, such as loss of consciousness or newly developed focal neurological deficit, including aphasia, hemiparesis, and disturbance of consciousness and no complicated cerebral infarction on MRIDWI; and Grade 3, <50% of the narrowing vessel diameter with the appearance of clinical symptoms with complicated cerebral infarction on MRIDWI (Fig 1).

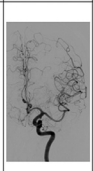
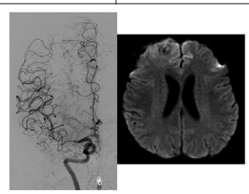
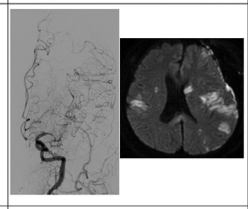
	Grade 0 spasm(-)	Grade 1	Grade 2	Grade 3
Angiography (51~99% of the narrowing)	-	+	+	+
Symptomatic	-	-	+	+
MRI DWI	-	-	-	+
Image				
Case	221	51	20	41

Figure 1. *Cerebral vasospasm grading and number of patients.*

Table 1. *Patient characteristics*

Spasm grade	0-3 (all cases)	Grade 0	Grade 1	Grade 2	Grade 3
Number of patient	333 cases	221	51	20	41
Sex (male)	123	87	14	11	11
Age (mean)	24-93 (mean 59.7)	(60.2)	(55.6)	(55.3)	(63.8)
H&K grade (nonsevere; 1-3, severe; 4, 5)	1: 37 cases 2: 123 cases 3: 69 cases 4: 64 cases 5: 40 cases (229,104)	(165, 56)	(45, 6)	(16, 4)	(3, 38)
Aneurysmal size (mm)	1.8-31 (mean 6.2)	(6.1)	(6.8)	(5.7)	(6.5)
Aneurysmal location (anterior circulation, posterior circulation + others)	ACA: 115 cases ICA: 87 cases MCA: 75 cases BA: 10 cases VA: 27 cases Others: 19 (287, 46)	(187, 34)	(43, 8)	(19, 1)	(38, 3)
GOS (at discharge) (good outcome; GR, MD, poor outcome; SD, VS, D)	GR: 91 cases MD: 51 cases SD: 122 cases VS: 49 cases D: 20 cases (142, 191)	(78, 143)	(45, 6)	(16, 4)	(3, 38)
Glucose/potassium ratio (SD)	49 (18)	48 (16)	50 (22)	49 (18)	58 (19)
Glucose (SD)	173 (52)	170 (49)	172 (52)	177 (62)	192 (60)
Potassium (SD)	3.6 (0.5)	3.6 (0.5)	3.6 (0.5)	3.6 (0.43)	3.4 (0.44)

Patient prognosis was evaluated at discharge and 3 months after discharge using the Glasgow Outcome Scale (GOS).[13] Good outcome was defined as good recovery (score 5) or moderate disability (score 4), and poor outcome as severe disability (score 3), vegetative state (score 2), or death (score 1).

Statistical Analysis

Statistical analysis was performed using SPSS for Mac (version 21.0; IBM Corp., Armonk, NY). Variables are expressed as mean ± standard deviation or number of patients (percentage), where appropriate. The relationship between cerebral vasospasm and cerebral infarction in the MRIDWI (group 3) and poor outcome (GOS poor outcome at discharge) groups was investigated. The normality of the data was evaluated using Shapiro-Wilk test. Normally distributed continuous and non-normally distributed variables were compared using Student's t test and the Mann-Whitney U test, respectively.

The correlation between vasospasm grade (0-3) and serum glucose/potassium ratio also was analyzed using Spearman's rank correlation coefficient. Comparisons in glucose/potassium ratio between good (GOS score 4 or 5) and poor (GOS scores 1-3) outcomes were examined using Mann-Whitney U test. First, univariate analysis was performed to determine statistically significant factors. Next, we performed multivariate logistic regression analysis for extracted variables, including age, sex, aneurysm size (mm), glucose/potassium ratio (>60; as reported in previous research [10]), WBC (μ/l) count, and CRP (mg/dl) level to identify the relationship between variables that were significantly associated with cerebral vasospasm and cerebral infarction in the MRIDWI (group 3) group. Differences were considered significant at $P < .05$.

Results

Patient characteristics are shown in Table 1.

We included the 333 patients (123 male, 210 female) with aneurysmal SAH underwent surgery at our institution. H&K grading[14] was 1, 2, 3, 4, and 5 in 37, 123, 69, 64, and 40 cases, respectively. Aneurysm ranged from 1.8 to 31 mm (mean 6.2 mm), and were located at the anterior communicating (115 cases), internal carotid (87), middle cerebral (75), basilar (10), and vertebral (27) arteries. Among 333 patients, 107 (32 %) were transferred to our hospital from elsewhere. The time from SAH to admission ranged from 1 hour to 16 days (mean 18.6 hours, standard deviation 47.1).

Postoperative angiography revealed cerebral vasospasm in 112 patients (33.6%; Grade 1, 51 cases; Grade 2, 20 cases; Grade 3, 41 cases; Fig 1).

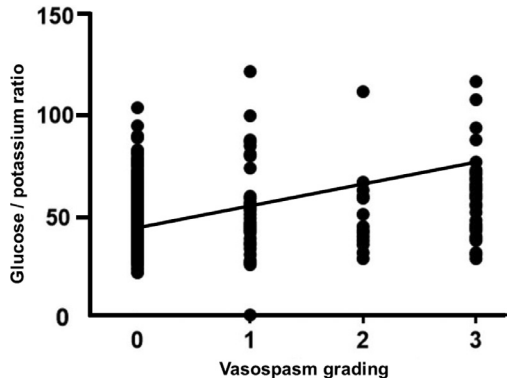


Figure 2. *Scatterplot showing the increased serum glucose/potassium ratio in a vasospasm grading- dependent manner (Spearman's r = 0.1207, P = .0279).*

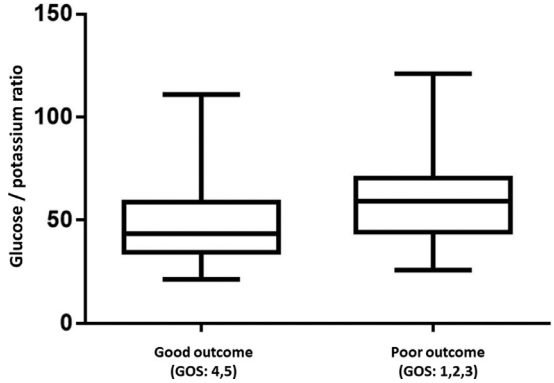


Figure 3. *Box-and-whiskers plot shows that the serum glucose/potassium ratio is significantly greater in the GOS poor than in the good outcome group (P < .0001).*

Significant correlations existed between the ischemic complication due to cerebral vasospasm (Grade 3) and glucose/potassium ratio ($P < .0001$), glucose ($P = .016$), and potassium ($P = .0017$). Serum glucose/potassium ratio was elevated in the cerebral vasospasm (grades 0-3) dependent manner (Spearman's $r = 0.1207$, $P = .0279$; Fig 2).

According to GOS score at discharge, 185 cases (55.5%) had a poor outcome (GOS scores 1-3). Serum glucose/potassium ratio was significantly correlated with poor outcome (GOS scores 1-3; Fig 3) and age ($P < .0001$), serum glucose/potassium ratio ($P < .0001$), glucose ($P < .0001$), potassium ($P = .0004$), WBC ($P = .0012$), cerebral infarction due to cerebral vasospasm ($P < .0001$), and H&K severe grade ($P < .0001$; Tables 2 and 3).

There was a statistically significant correlation between glucose/potassium ratio ($P < .0001$), glucose ($P = .0016$), and potassium ($P = .0017$) in univariate analysis.

Multivariate logistic regression analyses showed significant correlations between cerebral infarction due to cerebral vasospasm (grade 3) and serum glucose/potassium ratio ($P = .018$), glucose ($P = .027$), and potassium ($P = .052$; Table 4).

Discussion

In the present study, the serum glucose/potassium ratio in cases of aneurysmal SAH was significantly associated with cerebral infarction due to cerebral vasospasm and vasospasm grade. In addition, the serum glucose/potassium ratio was elevated in the poor (GOS scores 1-3) compared with that in the good (GOS score 4 or 5) outcome groups.

Aneurysmal SAH is difficult to treat because not only surgical strategy but also perioperative management is required. Especially in the case of cerebral vasospasm, despite a good clinical postoperative course, patients achieve poor progress due to cerebral vasospasm. Therefore, prevention of ischemic complications because of cerebral vasospasm is especially important to improve prognosis after aneurysmal SAH. Nakae et al[5] reported that transcranial Doppler ultrasonography is a useful screening tool for cerebral vasospasm. Ibrahim and Macdonald[15] reported that electrocardiographic changes are associated with vasospasm. Rosen and Macdonald[16] reviewed the advantage of neurological grading. These

Table 2. *Results of statistical analysis of the risk factors for cerebral infarction due to cerebral vasospasm in aneurysmal SAH*

		Cerebral infarction due to cerebral vasospasm		
Variable	Total	(−) n = 292	(+) n = 41	*P* value
Mean age, yr (SD)	59.7 (13.6)	59.7 (13.5)	63.9 (14.4)	.05
Sex, male (%)	123 (36.9)	111 (38)	12 (29.3)	.31
Aneurysm location (posterior circulation) (%)	37 (11.1)	35 (12)	2 (4.9)	.29
Aneurysm size (mm) (SD)	8.5 (4.4)	7 (3.9)	10.5 (4.4)	.65
Fisher group 3 (%)	298 (89)	263 (78)	35 (85)	.411
Glucose/potassium ratio (SD)	49.8 (18.4)	48.5 (17)	58.5 (19)	**.0001**
Glucose (mg/dl) (SD)	185 (52)	170 (50)	193 (60)	**.016**
Potassium (mEq/l) (SD)	3.58 (0.5)	3.62 (0.5)	3.36 (0.43)	**.0017**
WBC (μ/l) (SD)	11784 (7886)	11708 (8267)	12319 (4358)	.1434
CRP (mg/dl) (SD)	0.51 (1.52)	0.49 (1.51)	0.67 (1.57)	.5483
H&K grade (severe 4, 5) (%)	104 (31.2)	88 (30)	16 (39)	.2812

Data are expressed as number of patients (%), unless otherwise indicated.
Variables showing significant difference by univariate analysis ($P < .05$) are indicated by boldface.

Table 3. *Results of statistical analysis of the risk factors for poor outcome in aneurysmal SAH*

Variable	Total	Good outcome (GOS: GR, MD)	Poor outcome (GOS: SD, VS, D)	*P* value
Mean age, yr (SD)	59.7 (13.6)	53.5 (12.1)	64.7 (12.8)	**<.0001**
Sex, male (%)	123 (36.9)	58 (41)	65 (34)	.2089
Aneurysm location (posterior circulation) (%)	37 (11.1)	17 (11.9)	20 (10.5)	.7256
Aneurysm size (SD)	6.3 (3.9)	5.8 (3.1)	6.8 (4.5)	.154
Fisher group 3 (%)	298 (89)	130 (87)	168 (90)	.4725
Glucose/potassium ratio (SD)	49.8 (18.4)	42.1 (15.3)	55.8 (18.5)	**<.0001**
Glucose (SD)	185 (52)	152 (42)	190 (52)	**<.0001**
Potassium (SD)	3.58 (0.5)	3.68 (0.45)	3.51 (0.53)	**.0004**
WBC (SD)	11784 (7886)	10565 (3752)	12751 (9925)	**.0012**
CRP (SD)	0.51 (1.52)	0.34 (0.71)	0.65 (1.93)	.5795
Spasm grade 1 (angiography) (%)	51 (15)	45 (20)	6 (13)	.4063
Spasm grade 2 (symptomatic, CI−) (%)	20 (6)	16 (8)	4 (9)	.7677
Spasm grade 3 (symptomatic, CI+) (%)	41 (12.3)	3 (2.1)	38 (19.9)	**<.0001**
H &K grade (severe 4, 5) (%)	104 (31)	18 (12)	86 (46)	**<.0001**

Data are expressed as number of patients (%), unless otherwise indicated.
Variables showing significant difference by univariate analysis ($P < .05$) are indicated by boldface.

screening tools are especially useful, although their efficacy has limitations; some cases of cerebral infarction due to vasospasm have occurred.

On the other hand, biomarkers, such as CRP,[8] brain natriuretic peptide,[17] nitrous oxide inhibitor as asymmetric and symmetric dimethylarginines,[18] and peroxiredoxin 2 in patient cerebrospinal fluid,[19] have been correlated with delayed cerebral vasospasm recently. However, unfortunately, few reliable prediction factors for the occurrence of cerebral vasospasm have few reported, and commonly used biomarkers have failed to predict cerebral vasospasm and resulting cerebral infarction effectively.[20]

In aneurysmal SAH cases, sympathetic nervous activation occurs; therefore, excessive catecholamine, such as adrenaline, noradrenaline, and dopamine, are secreted.[21] Increased catecholamine levels are associated with cardiac complications, pulmonary cardiac edema, or arrhythmia,[22] and these complications influence the prognosis of aneurysmal SAH. Meanwhile, massive catecholamine levels also affect vascular smooth muscle contraction, a phenomenon that that has been related to an imbalance between vasodilator and vasoconstriction mediators.[23] Recently, ischemic complications due to cortical spreading depression and microcirculatory dysfunction have been reported in spite of vasospasm in large vessels.[24] Past clinical reports showed that endothelial dysfunction due to a lack of nitric oxide may play an important role in the development of this pathology.[25,26]

Serum glucose values have been correlated with cerebral metabolic distress, aneurysmal SAH, and poor outcome.[27] Huang et al[28] reported that hyperglycemia exacerbated cerebral vasospasm in a rat model of SAH.

Catecholamines, glucagon, and corticosteroids are primary glycol-regulatory hormones implicated in the hyperglycemic reaction.[29,30] Catecholamines are particularly important after injury and stress because they increase glucagon secretion and inhibit insulin secretion.[31]

Potassium is stored mostly within the cells, and its transportation is controlled by active cellular uptake of potassium through the cell membrane and adenosine triphosphatase sodium/potassium pump (Na+/K+-ATPase). Catecholamine, B2 adrenergic hormones, and insulin regulate Na+/K+-ATPase and result in a decrease in serum potassium level.[32] Epinephrine-induced hypokalemia results from stimulation of a β-adrenoceptor linked to membrane Na/K ATPase causing potassium influx.[33] In addition, aneurysmal SAH has a high serum glucose value by excessive catecholamine secretion as mentioned above; therefore, this situation promoted secretion of insulin and serum potassium entry into the cells.

In our study, the serum glucose/potassium ratio was significantly associated with cerebral infarction due to cerebral vasospasm and vasospasm grade. Therefore, serum glucose/potassium ratio is reflective of excessive catecholamine and may predict the occurrence of cerebral vasospasm. In addition, glucose/potassium ratio was

Table 4. *Multivariate logistic regression analysis for risk factors of cerebral vasospasm in aneurysmal SAH*

Variable	OR (95% CI)	*P* value
Age >60		.267
Glucose/potassium ratio >60	5.6 (0.98-56)	**.043**
Fisher		.57
Glucose and potassium ratio		**.018**
Glucose		**.027**
Potassium		**.052**

Abbreviations: CI, confidence interval; OR, odds ratio.
Variables showing significant difference by univariate analysis ($P < .05$) are indicated by boldface.

more useful than simple glucose and potassium by multivariate logistic regression. Perioperative treatment must be aggressive, such as with administration of a β blocker,[34] nimodipine,[35] and edaravone,[36] in patients with an elevated serum glucose/potassium ratio.

Limitation

This study had several limitations. (1) We did not investigate serum endocrine levels, such as catecholamine, glucagon, and corticosteroids; therefore, the real cause of the high serum glucose/potassium ratio in patients with severe aneurysmal SAH was not clear. (2) In the current study, there were no cases of cerebral ischemic complication due to cortical spreading depression or microcirculatory dysfunction despite vasospasm in large vessels. Moreover, we defined spasm grading originally; however, we have to carefully analyze focusing more on this pathology during postoperative course. (3) Our analysis was retrospective and from a single center. A prospective and multicenter trial is needed to support our claim in the future.

Conclusion

Our study shows, for the first time to our knowledge, that the serum glucose/potassium ratio was correlated with the incidence of cerebral infarction due to cerebral vasospasm and vasospasm grade. The serum glucose/potassium ratio may be a useful biomarker for the occurrence of cerebral vasospasm, and we must watch carefully for vasospasm in the case of high serum glucose/potassium levels. Further studies with larger cohorts are needed to verify our claim.

Conflicts of Interest

None of the authors have any conflicts of interest.

Ethical Approval

This study was approved by Chiba Hokusoh Hospital Research Ethics Committee, Chiba, Japan.

Informed Consent

All patients have consent to submission of this paper.

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