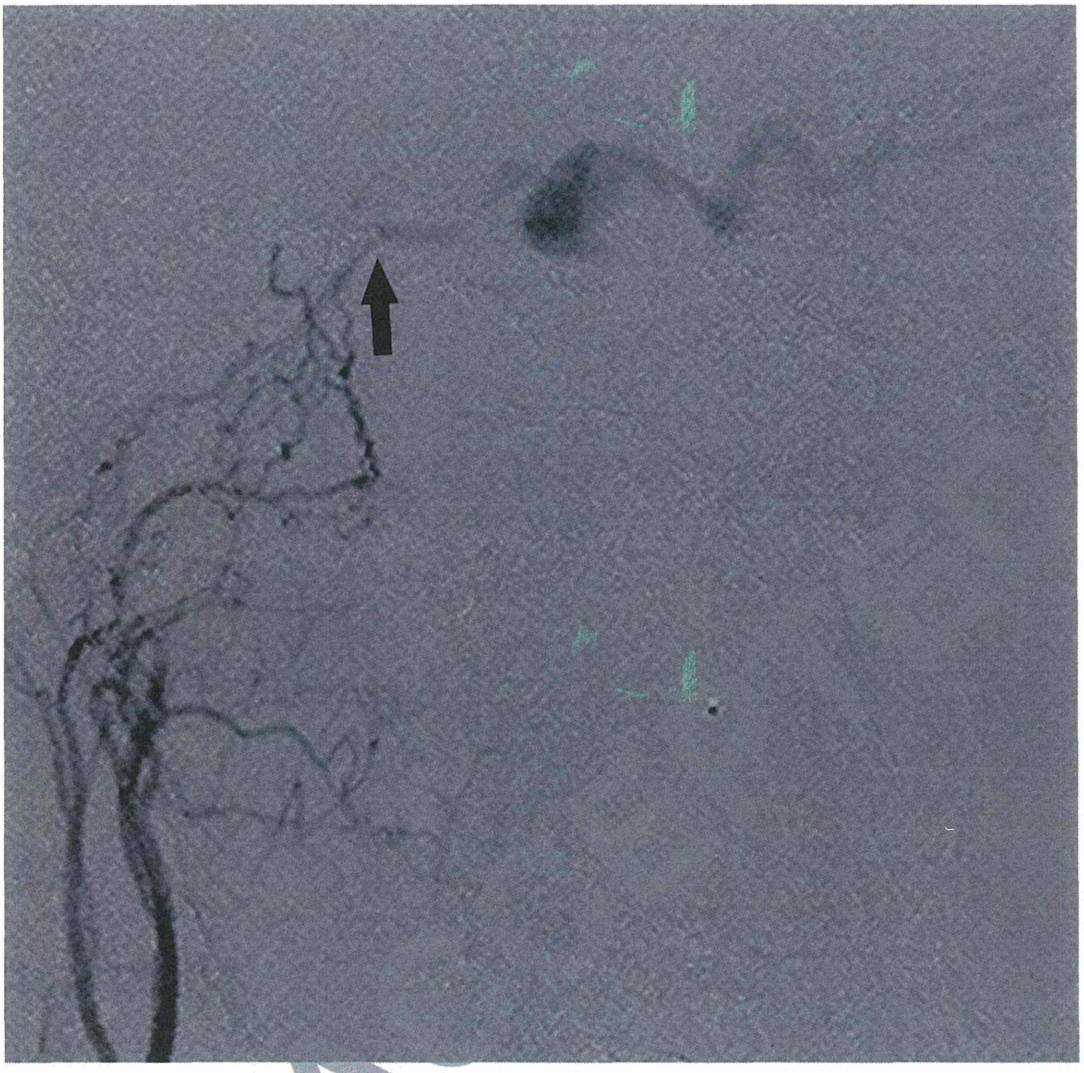

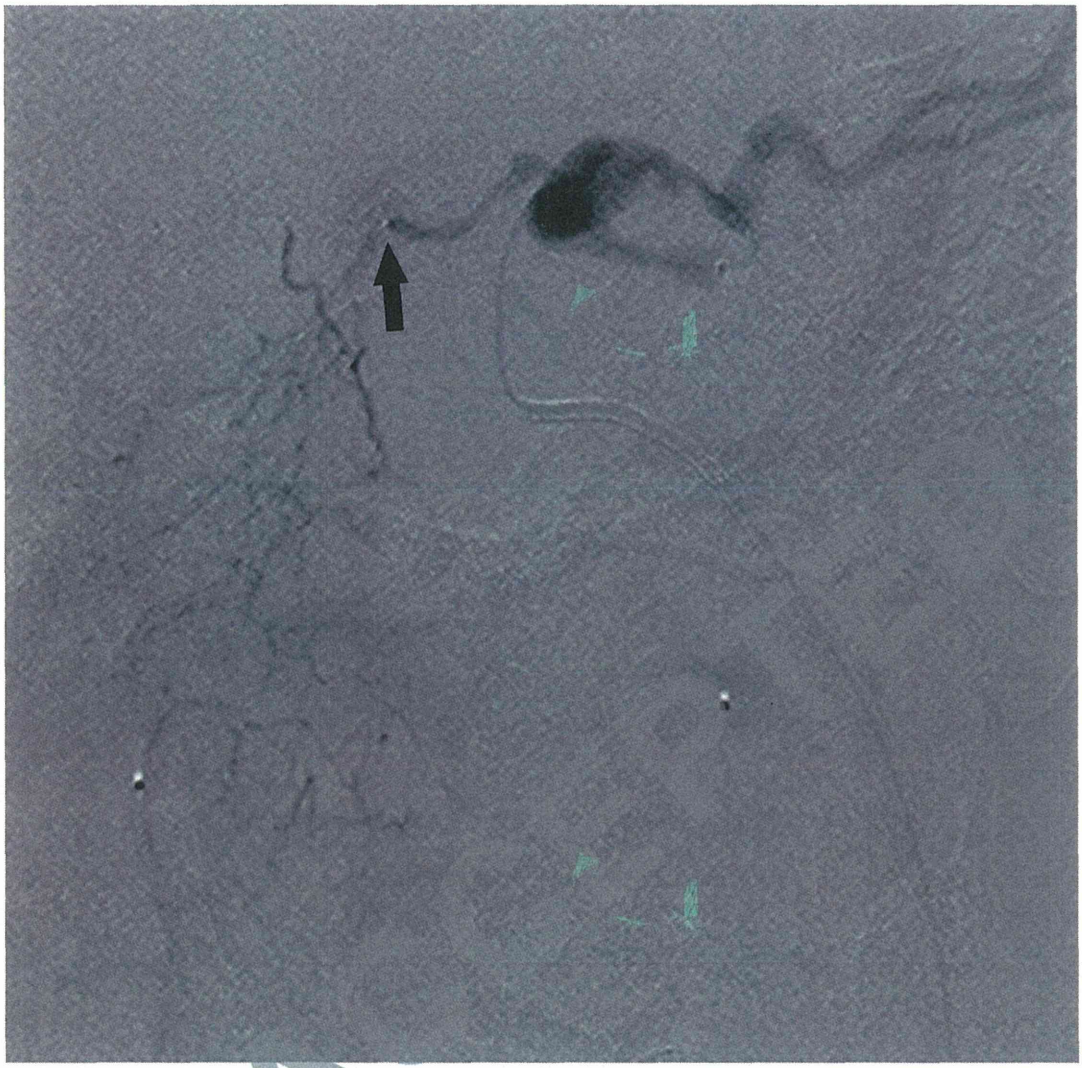

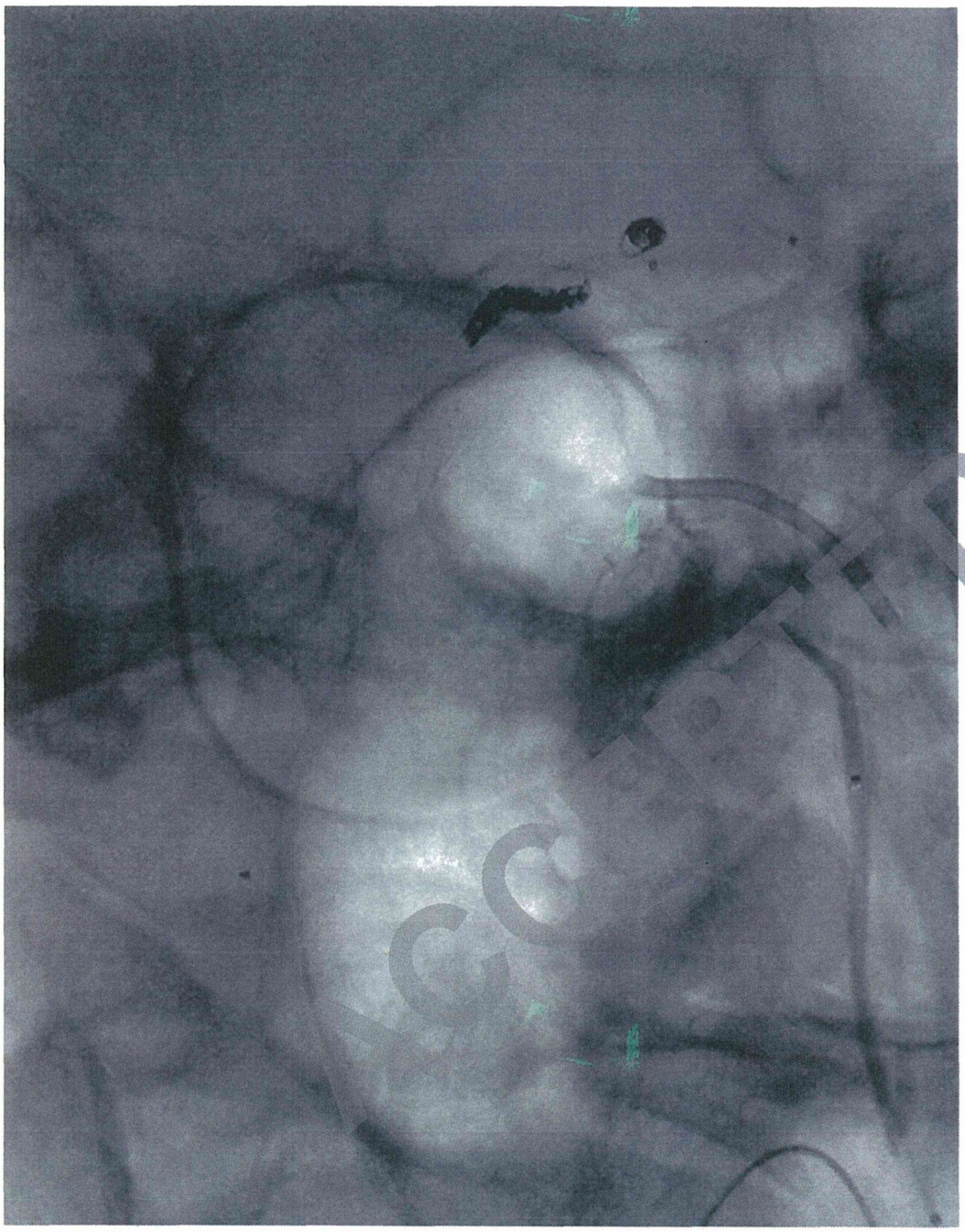

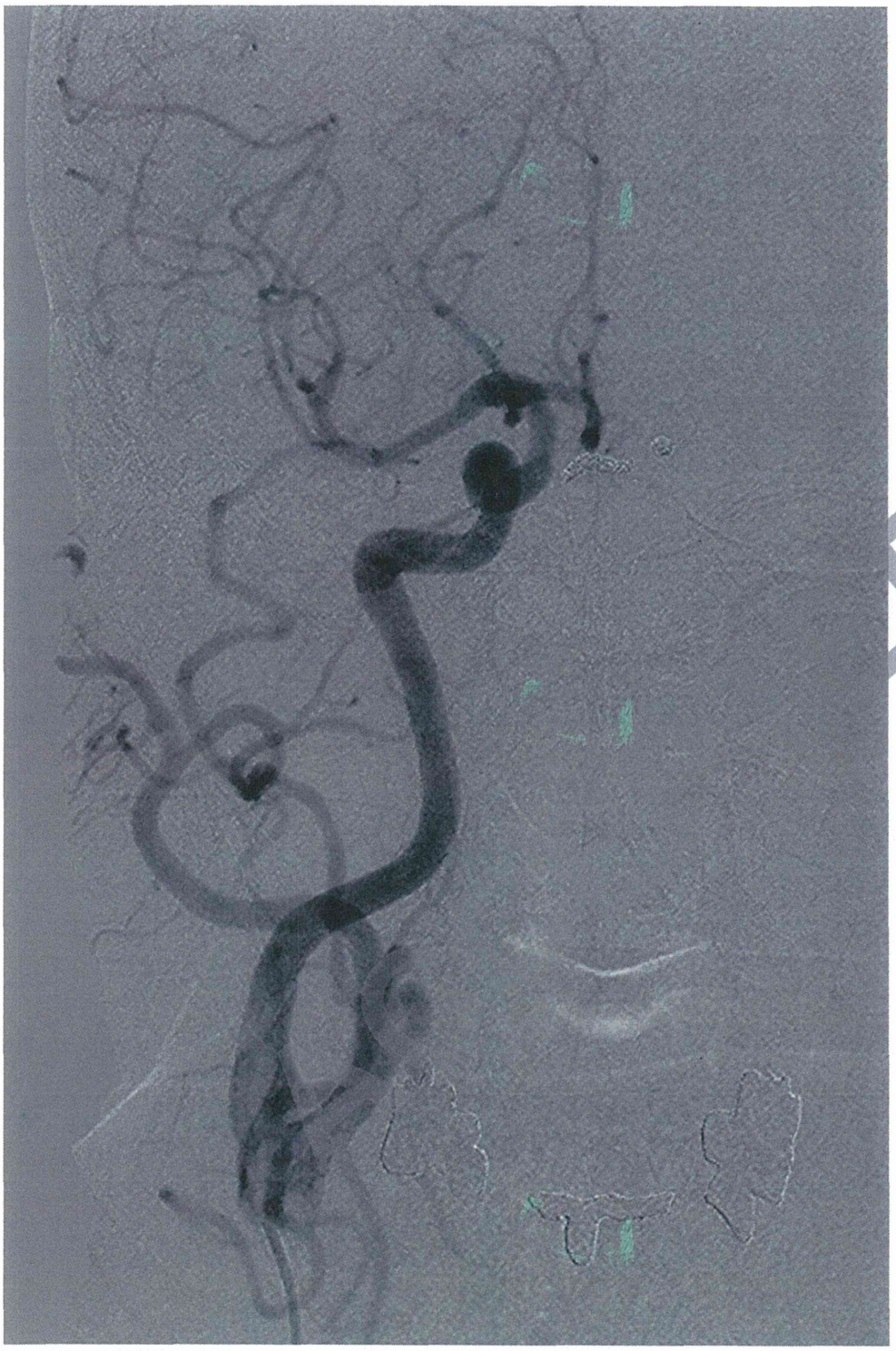

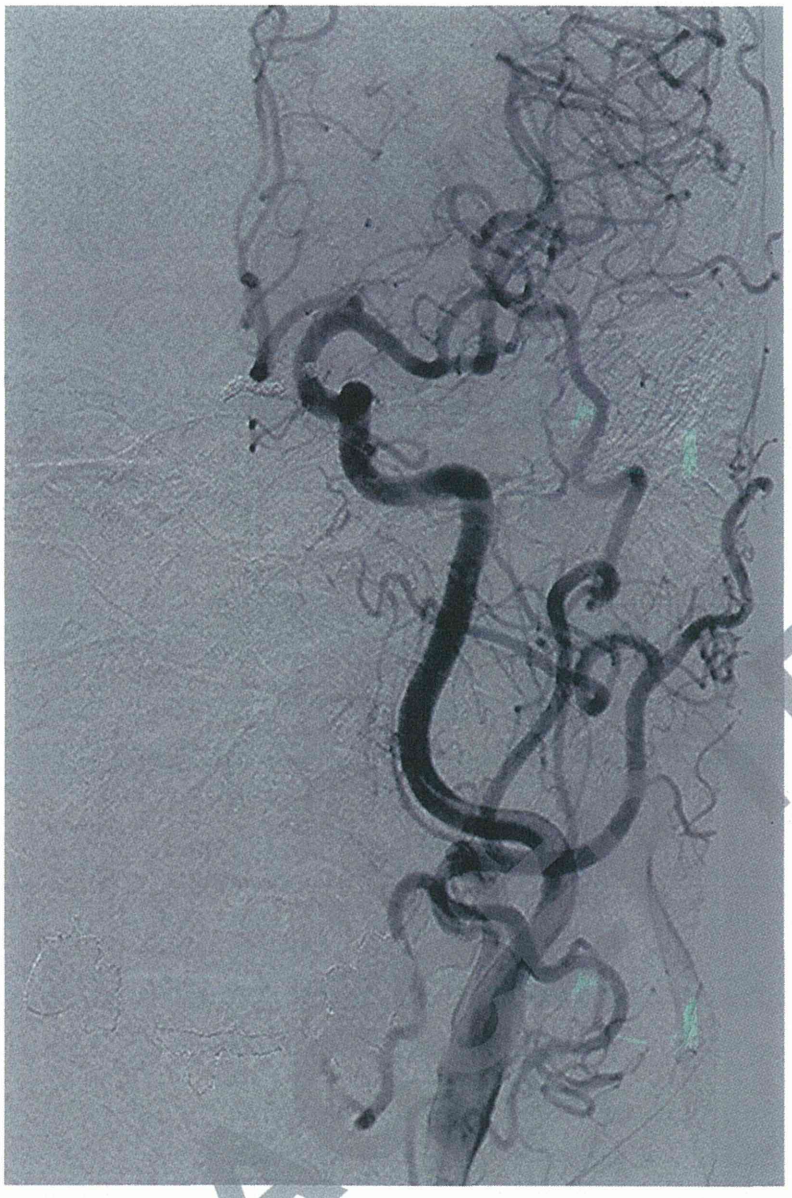

Haptoglobin Phenotype Predicts Cerebral Vasospasm and Clinical Deterioration after Aneurysmal Subarachnoid Hemorrhage

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Vasospasm (VS) and delayed cerebral ischemia (DCI) after subarachnoid hemorrhage (SAH) are thought to greatly affect prognosis. Haptoglobin (Hp) is a hemoglobin-binding protein expressed by a genetic polymorphism (1-1, 2-1, and 2-2). Our objects were to investigate whether the Hp phenotype could predict the incidence of cerebral infarction, favorable outcome, clinical deterioration by DCI, and angiographical VS after aneurysmal SAH. Ninety-five consecutive patients who underwent clipping or coil embolization were studied. Favorable functional outcome was defined as a modified Rankin Scale score of 0-2 at 3 months. Angiographical VS was diagnosed based on cerebral angiography findings performed between days 7 and 10 after SAH. The Hp 2-2 group had a significantly greater risk of angiographical VS than that of Hp 2-1 and 1-1 groups combined on univariate (odds ratio [OR]: 3.60, confidence interval [CI]: 1.49-8.67, $P = .003$) and multivariate logistic regression analyses after being adjusted for age, sex, Fisher groups, and other risk factors (OR: 3.75, CI: 1.54-9.16, $P = .004$). The Hp 2-2 group also showed the tendency of a greater risk of clinical deterioration by DCI with marginal significance on univariate and age- and sex-adjusted analyses (univariate OR: 2.46, CI: .90-6.74, $P = .080$; age- and sex-adjusted OR: 2.46, CI: .89-6.82, $P = .080$) but not after being adjusted for other multiple risk factors. The Hp 2-2 group was not associated with the favorable 3-month outcome and cerebral infarction (univariate: $P = .867$, $P = .209$; multivariate: $P = .905$, $P = .292$). The Hp phenotype seems to be associated with a higher rate of angiographical VS and clinical deterioration by DCI but does not affect the incidence of cerebral infarction and favorable outcome. **Key Words:** Haptoglobin—subarachnoid hemorrhage—vasospasm—clinical deterioration by DCI.

Introduction

Vasospasm (VS) and delayed cerebral ischemia (DCI) after subarachnoid hemorrhage (SAH) are serious complications that induce cerebral infarction in the acute phase, and along with state of consciousness and age at the time of hemorrhage, the occurrence of VS and DCI is thought to

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greatly affect prognosis.[1-3] However, there is currently no definitive predictor for the occurrence of VS and DCI, and only hematoma volume and distribution on computed tomography (CT) scans are considered to be correlated with the occurrence of VS.[4-6] In 1991, Macdonald and Weir[7] reported the pathogenetic mechanisms by which oxyhemoglobin (Oxy Hb) affects cerebral arteries. Oxy Hb is a well-known spasmogen and this study focused on Haptoglobin (Hp), which neutralizes Oxy Hb.

There have been various reports in recent years on the expression of disease depending on the Hp phenotype (3 phenotypes: 1-1, 2-1, and 2-2), with Hp 1-1 being correlated with leukemias[8] and Hp 2-1 and Hp 2-2 being correlated with diabetic vascular disorder and venous thrombosis.[9,10]

Kaisorn et al,[11] using a murine model of SAH, reported a significantly higher incidence of cerebral VS and decreased activity after hemorrhage in mice with the Hp 2-2 phenotype. Borsody et al,[12] whose subjects were 32 patients with Fisher grade 3 SAH, reported significantly more VS in patients with Hp 2-1 and 2-2 phenotypes, which have α2 light chains on transcranial Doppler ultrasound, but no significant association was established with cerebral angiography.

However, no previous studies systematically determine the impact of the Hp phenotype on the incidence of cerebral infarction, functional outcome, clinical deterioration by DCI, and angiographical VS after aneurismal SAH. The purpose of this study was to determine whether the Hp phenotype may predict the occurrence of cerebral infarction, clinical deterioration by DCI, angiographical VS, and functional outcome after aneurysmal SAH.

Methods

Subjects were 95 consecutive patients with SAH (excluding cases of chronic phase treatment or death) as a result of ruptured cerebral aneurysm who underwent clipping or coil embolization in the acute onset phase at the National Cardiovascular Center (National Cerebral and Cardiovascular Center as of April 2010) between December, 2008, and July, 2011. The severity of SAH was judged in all cases by the Hunt and Kosnik grade at the time of onset and hematoma volume was evaluated by CT scans using Fisher groups within 48 hours of admission to the hospital. Subsequently, under general anesthesia, angiography was performed. After identifying the ruptured cerebral aneurysm, clipping or coil embolization was carried out on the day of onset or the following day.

Sample Collection

Sampling of blood specimens was done on the day of onset or the following day. Approval for blood collection was received from our Institutional Review Board and informed consent was obtained from each patient or their families at the time of sampling. Blood specimens were shipped to SRL, Inc. (Tachikawa, Japan) for Hp typing. The phenotype was then identified using a quantitative method (nephelometric assay, reference values: 1-1, 130-327; 2-1, 103-341; 2-2, 41-273 mg/dL). The sensitivity and specificity of a nephelometric assay compare quite well of an electrophoretic determination.[13] The treating physician was kept blind of the assay results.

Evaluation and Prevention of VS and DCI

Diagnosis of VS was based on cerebral angiography findings in all patients. Cerebral angiography was performed twice, on the day of onset and between days 7 and 10 postictus. Vessel diameters of the bilateral anterior cerebral and middle cerebral arteries (A1 and M1 regions) were compared, and narrowing of these vessels of greater than or equal to 50% compared with the day of onset was diagnosed with angiographical VS.[12] Evaluation of the cerebral angiograms was performed without knowledge of the Hp phenotype. Patients who developed focal neurological symptoms (such as hemiparesis, aphasia, apraxia, hemianopsia, or neglect) or a decrease of at least 2 points on the Glasgow Coma Scale were diagnosed with clinical deterioration by DCI after other causes such as hydrocephalus and electrolyte imbalances were excluded by means of clinical assessment, CT or magnetic resonance imaging (MRI), and laboratory tests. Cerebral infarction was defined as new ischemic lesions on CT or MRI within 6 weeks after SAH, which were not present on CT or MRI between 24 and 48 hours after aneurysm obliteration, to exclude other causes such as surgical clipping or endovascular treatment.

Postoperatively, blood pressure was managed to maintain normotension and circulating plasma volume was kept normovolemia (central venous pressure was maintained at ≥5 cm H_2O). If clinical deterioration caused by DCI developed, induced hypertension and hypervolemia were introduced. Until 2 weeks after SAH, all the patients were also treated with drip infusion of fasudil hydrochloride, and cisternal or spinal drainage was done with the aim of facilitating evacuation of the subarachnoid clot. Arterial injection of fasudil hydrochloride (30 mg) was done at the site of narrowing for VS with clinical deterioration. To determine the final prognosis, an evaluation was done using the modified Rankin Scale at the time of discharge and after 3 months. All these outcome measures were evaluated by separate neurosurgeons who do not know the patient and Hp phenotype.

Statistical Analysis

The normalcy of distribution of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables were normally distributed and were compared across Hp categories using a 1-way analysis of variance. Categorical variables were compared using the chi-square test.

Univariate and multivariate logistic regression analyses were applied to correlate the Hp phenotype with the risk of angiographic VS, clinical deterioration by DCI, favorable 3-month outcome, and cerebral infarction. Age, sex, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, Hunt and Kosnik grade greater than or equal to IV, and Fisher group greater than or equal to 3 were included in the multivariate model for the adjustment. The Hp 2-2 group was compared with the Hp 2-1 and 1-1 groups because the Hp 1-1 group was relatively small ($n = 7$). All tests were 2 tailed, with differences reported as significant if P less than .05. STATA version 12 (StataCorp LP, College Station, TX) was used for all statistical analyses.

Results

The 95 subjects (53 women) ranged in age from 24 to 92 years (mean 62.1 years; Table 1). The Hp phenotype was Hp 1-1 in 7 patients (7.4%), Hp 2-1 in 39 patients (41.1%), and Hp 2-2 in 49 patients (51.6%). The Hunt and Kosnik grade at the time of onset was I in 18.9%, II in 25.2%, III in 14.7%, IV in 16.8%, and V in 24.4% of patients. Fisher group was 1 in 1.1%, 2 in 8.4%, 3 in 69.5%, and 4 in 21.0% of patients. There were no significant differences between the Hp phenotype and patient characteristics and severity of SAH except for a higher incidence of dyslipidemia in Hp 2-1. The location of the aneurysm showed a general distribution; it was located in the anterior communicating artery in 30.1% of patients, posterior communicating artery in 20.0% of patients, middle cerebral artery in 18.9% of patients, internal carotid artery in 11.6% of patients, anterior cerebral artery in 5.3% patients, and posterior circulation in 13.7% of patients. The treatment for these aneurysms was clipping in 71.6% of patients, coil embolization in 23.2% of patients, and trapping in 5.2% of patients.

Angiographical VS and the Hp Phenotype

The overall incidence of angiographical VS was 37.9%. The incidence of angiographical VS based on the Hp phenotype (1-1: 28.6%, 2-1: 20.5%, 2-2: 53.1%) was depicted in Figure 1. Univariate analysis (Table 2) showed that angiographical VS was more significantly associated with Hp 2-2 than with Hp 2-1 and 1-1 combined (odds ratio [OR]: 3.60, confidence interval [CI]: 1.49-8.67, $P = .003$), and the association between angiographical VS and hypertension was marginally significant (OR: .47, CI: .20-1.08, $P = .070$). Age- and sex-adjusted and multivariate analyses (Table 3) showed that Hp 2-2 remained a significant risk factor for angiographical VS (age- and sex-adjusted OR: 3.75, CI: 1.54-9.16, $P = .004$, multivariate OR: 3.00, CI: 1.13-7.91, $P = .003$).

Clinical Deterioration by DCI and the Hp Phenotype

The overall incidence of clinical deterioration by DCI was 23.2%. The incidence of clinical deterioration by DCI based on the Hp phenotype (1-1: 28.6%, 2-1: 12.8%, 2-2: 30.6%) was depicted in Figure 2. Univariate analysis (Table 2) and age- and sex-adjusted analysis demonstrated that the Hp 2-2 group also showed a tendency of greater risk of clinical deterioration by DCI with marginal significance in univariate and age- and sex-adjusted analyses (univariate OR: 2.46, CI: .90-6.74, $P = .080$; age- and sex-adjusted OR: 2.46, CI: .89-6.82, $P = .080$; Tables 2 and 3). However, after adjustment of other multiple risk factors, the OR of clinical deterioration became insignificant ($P = .217$; Table 3).

Cerebral Infarction within 6-Week Postictus and the Hp Phenotype

The overall incidence of clinical deterioration by cerebral infarction was 18.9%. The incidence of cerebral infarction based on the Hp phenotype (1-1: 14.3%, 2-1: 12.8%, 2-2: 24.5%) was depicted in Figure 3. On univariate (Table 2), age- and sex-adjusted, and multivariate analyses (Table 3), the Hp 2-2 group showed no significant tendency of greater risk of cerebral infarction within 6 weeks.

Favorable Outcome at 3 Months and the Hp Phenotype

After 3 months, the modified Rankin Scale score was 0 in 34.7%, 1 in 11.6%, 2 in 13.7%, 3 in 13.7%, 4 in 11.6%, 5 in

Table 1. *Demographics, medical history, and severity of subarachnoid hemorrhage based on the haptoglobin phenotype*

	Hp 1-1 ($n = 7$)	Hp 2-1 ($n = 39$)	Hp 2-2 ($n = 49$)	P value
Age (mean ± SD)	64.9 ± 15	60.9 ± 15	62.8 ± 13	.708
Male, *n* (%)	3 (42.9)	17 (43.6)	22 (44.9)	.990
Hypertension, *n* (%)	4 (57.1)	25 (64.1)	23 (46.9)	.270
Dyslipidemia, *n* (%)	1 (14.3)	8 (20.5)	2 (4.1)	.048*
Diabetes mellitus, *n* (%)	0	4 (10.3)	5 (10.2)	.484
Smoking, *n* (%)	3 (42.9)	5 (12.8)	11 (22.5)	.178
Coronary artery disease, *n* (%)	0	1 (2.6)	3 (6.1)	.523
Hunt and Kosnik grade IV-V, *n* (%)	4 (57.1)	18 (46.2)	17 (35.4)	.411
Fisher group 3-4, *n* (%)	6 (85.7)	35 (89.7)	45 (91.8)	.446

*Statistically significant, $P < .05$.

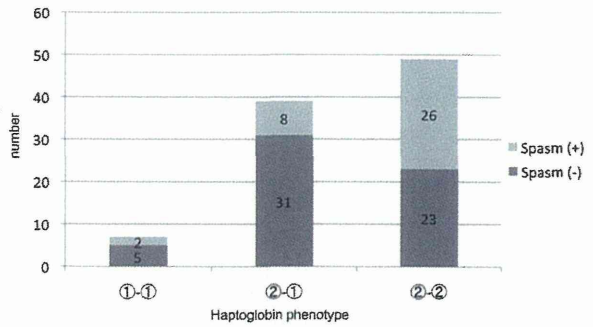

Figure 1. *The overall incidence of angiographical VS was 37.9%. A comparison of 3 groups revealed a significantly higher incidence of angiographical VS in Hp 2-2 patients than that of Hp 1-1 or Hp 2-1 patients* (P = .003). *Abbreviation: VS, vasospasm.*

11.6%, and 6 in 3.1%. The overall incidence of favorable outcome at 3 months was 60.0%. The incidence of favorable outcome based on the Hp phenotype (1-1: 42.9%, 2-1: 64.1%, 2-2: 59.2%) was depicted in Figure 4. On univariate analysis (Table 2), Fisher group was the only significant factor of favorable outcome ($P = .026$). On univariate (Table 2), age- and sex-adjusted, and multivariate analyses (Table 3), the Hp 2-2 group showed no significant tendency of favorable outcome.

Hydrocephalus

Patients who required a ventriculoperitoneal shunt because of the development of hydrocephalus and worsening neurological symptoms were also investigated. The incidence of hydrocephalus was 28.6% in Hp 1-1 patients, 28.2% in Hp 2-1, and 40.8% in Hp 2-2 patients. There was no significant difference between Hp 2-2 and other groups ($P = .478$).

Discussion

VS and DCI are the major factors in poor prognosis that are equivalent to the severity at the onset of hemorrhage.[1-3] Although studies of various biomarkers as predictive factors have been reported in recent years, they are still not definitive.[14,15] The purpose of this prospective study was to systematically determine whether the Hp phenotype may predict the occurrence of cerebral infarction, clinical deterioration by DCI, angiographical VS, and functional outcome after aneurysmal SAH. In the present study, we clearly demonstrated, for the first time, that the Hp 2-2 phenotype has an increased risk of angiographical VS diagnosed on cerebral angiography, a gold standard, on univariate, age- and sex-adjusted, and multivariate analyses, and a relatively weak association between Hp 2-2 and clinical deterioration by DCI in the largest human subjects. On the other hand, cerebral infarction and functional outcome, 2 main outcome measures to investigate strategies to prevent DCI were not affected based on the Hp phenotype.

Table 2. *Univariate analysis in angiographical vasospasm, clinical deterioration by DCI, cerebral infarction, and favorable 3-month outcome*

Variables	Angiographical vasospasm			Clinical deterioration by DCI			Cerebral infarction			Favorable outcome		
	OR	CI	*P* value	OR	CI	*P* value	OR	CI	*P* value	OR	CI	*P* value
Age (≤60 versus >60 y)	1.73	.75-3.98	.194	.67	.26-1.77	.420	.62	.22-1.77	.367	5.96	2.36-15.00	<.0001
Sex (male versus female)	.94	.41-2.15	.879	.65	.25-1.75	.395	.42	.14-1.28	.112	.57	.25-1.30	.177
Hypertension	.47	.20-1.08	.070	.62	.24-1.60	.319	.79	.28-2.21	.654	1.15	.51-2.63	.737
Diabetes	1.28	.32-5.13	.724	.94	.18-4.91	.944	2.37	.53-10.50	.279	.30	.07-1.27	.090
Dyslipidemia	.55	.14-2.23	.388	.71	.14-3.57	.670	.94	.19-4.80	.945	1.19	.32-4.38	.793
Coronary artery disease	1.60	.22-11.90	.647	1.11	.11-11.30	.930	4.69	.61-35.80	.151	.65	.09-4.86	.680
Smoking	2.02	.73-5.57	.176	1.24	.39-3.93	.718	.44	.09-2.11	.269	.90	.32-2.49	.835
Hunt and Kosnik (IV-V versus I-III)	.57	.24-1.36	.204	.83	.31-2.26	.719	1.16	.41-3.27	.777	.17	.07-.43	<.0001
Fisher group (3-4 versus 1-2)	1.31	.31-5.58	.714	6.63*	.37-118.50	.188	4.12*	.23-74.58	.376	.00*	.23-74.58	.027
Haptoglobin (2-2 versus 2-1,1-1)	3.60	1.49-8.67	.003	2.46	.90-6.74	.080	2.10	.66-6.70	.209	.93	.41-2.12	.867

Abbreviations: DCI, delayed cerebral ischemia; OR, odds ratio; CI, confidence interval.
*Odds ratios were calculated from 2 × 2 table with Yate's continuity correction for null cells.

Table 3. *Age- and sex-adjusted and multivariate analyses in angiographical vasospasm, clinical deterioration by DCI, cerebral infarction, and favorable 3-month outcome*

Variables	Angiographical vasospasm			Clinical deterioration by DCI			Cerebral infarction			Favorable outcome		
	OR	CI	*P* value	OR	CI	*P* value	OR	CI	*P* value	OR	CI	*P* value
Age- and sex-adjusted analysis												
Haptoglobin (2-2 versus 2-1, 1-1)	3.75	1.54-9.16	.004	2.46	.89-6.82	.083	2.10	.65-6.77	.214	.96	.37-2.54	.941
Multivariate analysis*												
Haptoglobin (2-2 versus 2-1, 1-1)	3.00	1.13-7.91	.003	2.01	.66-6.12	.217	2.10	.55-7.38	.292	.93	.28-3.13	.905

Abbreviations: DCI, delayed cerebral ischemia; OR, odds ratio; CI, confidence interval.
*Adjusted for age, sex, hypertension, DM, dyslipidemia, coronary artery disease, Hunt and Kosnik grade IV-V, and Fisher group 3-4.

Figure 2. *The overall incidence of clinical deterioration by DCI was 23.2%. The incidence of clinical deterioration by DCI was in 2 of 7 (28.6%) patients with Hp 1-1, 5 of 39 (12.8%) patients with Hp 2-1, and 15 of 49 (30.6%) patients with Hp 2-2. Abbreviation: DCI, delayed cerebral ischemia.*

Hp is a hemoglobin (Hb)-binding protein produced mainly in the liver. Free Hb is released when intravascular or extravascular hemolysis occurs. Free Hb promotes the production of free radicals (hydroxyl: OH-), which have a harmful effect on the vascular endothelium,[16] and blocks nitric oxide (NO), which causes vasodilation.[17] Hp quickly and very strongly binds to free Hb and is rapidly taken up in the liver.[18] This mechanism neutralizes the toxicity of free Hb and prevents the loss of Hb from the renal glomeruli.[19-21] The free Hb released during this hemolysis is reported to be closely related to the expression of angiographical VS,[7] and unless free Hb is quickly metabolized, it may increase the likelihood of VS.[22]

The basic structure of Hp consists of a tetramer in which 2 light chain polypeptides (α-chain) and 2 heavy chain polypeptides (β-chain) are bound. The α chain has 2 phenotypes, α1 and α2. Thus, depending on the combination, Hp is classified into 3 phenotypes: Hp 1-1, (α1β) × 2; Hp 2-1, (α1β) (α2β); and Hp 2-2, (α2β) × 2.[19] Javid[23] reported that the ability to bind Hb differs among the Hp phenotypes, with the Hb-binding ability strong in Hp 1-1, intermediate in Hp 2-1, and weak in Hp 2-2. Differences in this binding ability are expressed as

Figure 3. *The overall incidence of cerebral infarction within 6 weeks after SAH was 18.9%. The incidence of cerebral infarction was in 1 of 7 (14.3%) patients with Hp 1-1, 5 of 39 (12.8%) patients with Hp 2-1, and 12 of 49 (24.5%) patients with Hp 2-2. Abbreviation: SAH, subarachnoid hemorrhage.*

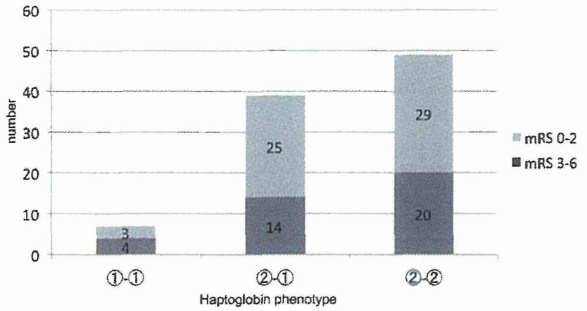

Figure 4. *The overall incidence of favorable outcomes after 3 months was 60.0%. The incidence of favorable outcomes was in 3 of 7 (42.9%) patients with Hp 1-1, 25 of 39 (64.1%) patients with Hp 2-1, and 29 of 49 (59.2%) patients with Hp 2-2.*

differences in the clearance of free Hb and may explain the higher expression of VS with Hp 2-2, which has a weak free Hb-binding ability. Levy et al[9] reported higher incidences of diabetic nephropathy in diabetic patients and restenosis after angioplasty for coronary artery lesions in Hp 2-1 and Hp 2-2 patients than in Hp 1-1 patients. In addition, Vormittag et al[10] reported that, in patients with deep vein thrombosis, Hp 2-2 was significantly more common than Hp 1-1 or Hp 2-1. Regarding the distribution of the Hp phenotype, the Hp 2-1 phenotype is the most common in Western countries (47%-55%), whereas the Hp 2-2 phenotype is more common in Asia (35%-55%).[24] Although Hp 1-1 is very uncommon in Asia, it has been reported in 10%-20% of people in Western countries, where Hp 2-1 is the most common phenotype.[24] This racial difference may make it difficult to apply the present results directly to people of other races, but the results of the present study were not contradictory to previous reports in Western populations and experimental animals.[11,12]

In this study, the Hp 2-2 phenotype has an increased risk of angiographical VS diagnosed on cerebral angiography and a relatively weak association between Hp 2-2 and clinical deterioration by DCI in the largest human subjects. Borsody et al[12] previously demonstrated using transcranial Doppler ultrasonography, which has a lower sensitivity and specificity to diagnose angiographic arterial narrowing, that VS was more common in the types that have an α2 subunit (Hp 2-1 and Hp 2-2) in the patients of Fisher group 3. Unfortunately, they did not provide conclusive data regarding the association between the Hp phenotype and angiographical VS on cerebral angiography, DCI, and the 2 major outcome measures, cerebral infarction and functional outcome. In this respect, the present study provided systematic data regarding the impact of Hp phenotype on critical outcome measures after SAH.

Although traditionally VS is thought to be the main cause for DCI, VS can be present without DCI and DCI can be present without VS.[25] Recently, Dhar et al[26] reported the relationship between angiographical VS and regional hypoperfusion in aneurysmal SAH using positron emission tomography. In this study, angiographical VS was associated with reductions in cerebral perfusion, but 66% of regions with hypoperfusion were supplied by vessels with no significant VS, and a low oxygen extraction fraction of .5 or more occurred more frequently outside territories with VS. The disparity of associations between the Hp phenotype and the 4 outcome measures described in this study may be explained by the presence of multifactorial causes of critical reductions in perfusion after SAH.

Another explanation is the total management for VS with clinical deterioration, including hypertensive therapy, continuous intravenous infusion of fasudil hydrochloride, and cisternal or spinal drainage. Because of a relatively small number of cases who underwent intra-arterial injection of fasudil hydrochloride, the definite contribution of intra-arterial injection of fasudil hydrochloride to the development of cerebral infarction and favorable functional outcome needs further investigation.

Strengths and Weakness of This Study

One strength of this study is that the diagnosis of angiographical VS was established using cerebral angiography in all cases after the Institutional Review Board approved this study protocol. Because the routine use of postoperative cerebral angiography between days 7 and 10 confers an additional risk, triaging patients at high risk of angiographical VS based on the Hp phenotype for cerebral angiography and timely use of intra-arterial infusion of fasudil hydrochloride may prevent the occurrence of asymptomatic, and symptomatic, cerebral infarction, especially in comatose patients.

Conclusions

The correlation between VS and DCI after SAH and the Hp phenotype was investigated. In individuals with the Hp 2-2 phenotype, VS was significantly more common and there was a tendency for clinical deterioration caused by DCI to develop. The ability to predict the development of VS and DCI in the early stage of SAH by investigating the Hp phenotype may help prevent the occurrence of symptoms and improve prognosis. In the future, it will be necessary to conduct studies with a larger number of subjects.

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