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Haptoglobin genotype and functional outcome after aneurysmal subarachnoid hemorrhage

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Abstract

Object—*Haptoglobin* allele heterogeneity has been implicated in differential reactive oxidant inhibition and inflammation. Haptoglobin α2-α2 has a lower affinity for binding hemoglobin, and when bound to hemoglobin, is cleared less easily by the body. The authors hypothesized that *haptoglobin α2-α2* genotype should be less protective for downstream injury after aneurysmal subarachnoid hemorrhage (aSAH) and should portend a worse outcome.

Methods—Patients with Fisher Grade 2 or higher aSAH were enrolled in the study. Genotyping for *haptoglobin* genotype was performed from blood and/or CSF. Demographic information, medical condition variables, and hospital course were abstracted from the medical record upon enrollment into the study. Outcome data (modified Rankin Scale score, Glasgow Outcome Scale score, and mortality) were collected at 3 months posthemorrhage.

Results—The authors enrolled 193 patients who ranged in age from 18 to 75 years. Only Caucasians were used in this analysis to minimize bias from variable *haptoglobin* allele frequencies in populations of different ancestral backgrounds. The sample had more women than

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men (overall mean age 54.45 years). *Haptoglobin α2* homozygotes were older than the other individuals in the study sample (57.27 vs 53.2 years, respectively; p = 0.02) and were more likely to have Fisher Grade 3 SAH (p = 0.02). *Haptoglobin α2-α2* genotype, along with Fisher grade and Hunt and Hess grade, was associated with a worse 3-month outcome compared to those with the *haptoglobin α1-α1* genotype according to modified Rankin Scale score after controlling for covariates (OR 4.138, p = 0.0463).

Conclusions—Patients with aSAH who carry the *haptoglobin α2-α2* genotype had a worse outcome. Interestingly, the presence of a single *α-2* allele was associated with worse outcome, suggesting that the haptoglobin α-2 protein may play a role in the pathology of brain injury following aSAH, although the mechanism for this finding requires further research. The *haptoglobin* genotype may provide additional information on individual risk of secondary injury and recovery to guide care focused on improving outcomes.

Keywords

haptoglobin; stroke; subarachnoid hemorrhage; vasospasm; genetic; hemoglobin; vascular disorders

A Neurysmal subarachnoid hemorrhage (aSAH) is a serious disease with a 40%–50% mortality rate.[18,21] In those patients surviving the initial hemorrhage, only 20% return to their pre-aSAH functioning capacity due to prolonged physical disabilities and cognitive deficits.[5,10] Haptoglobin (Hp) is an acute-phase protein that binds and clears free hemoglobin (Hgb), neutralizing its activity as a reactive oxidant species.[3,14,15,19] Genetic variation within the *HP* gene leads to functionally different isoforms.[7,13,20,22] The α chain in particular mediates important function to the protein as well as the variability in isoform performance.[13] The α-2 isoform has a weaker binding affinity for Hgb than the α-1 isoform and likely inhibits Hp-Hgb clearance due to its larger size.[6] This suggests that patients with the α-2 isoform should have increased propensity for reactive oxidant species formation that may consequently promote secondary injury and a worse recovery from aSAH. The purpose of this study was to determine if variability in the *HP* gene affects outcome in patients who experience aSAH. We hypothesize that patients with the *HP α2-α2* genotype will have worse outcome after aSAH compared with patients with the *α1-α1* or *α1-α2* genotypes.

Methods

This study was completed under University of Pittsburgh Institutional Review Board oversight. The specific comparison was a re-analysis of DNA material collected as part of an ongoing prospective trial in aSAH (NIH/NINR grant no. R0100439; principal investigators Sherwood and Poloyac). The specific enrollment criteria and methods for outcome determination have been published elsewhere.[1] Briefly, patients were recruited after admission to the Neurovascular Intensive Care Unit at the University of Pittsburgh Medical Center with a diagnosis of aSAH. All patients admitted to the Neurovascular Intensive Care Unit were screened for eligibility for this study based on the following criteria: 1) age 18–75 years and 2) angiography-based diagnosis of aSAH. For the present study we included only Caucasian patients with Fisher Grade 2 or higher hemorrhages (denoting substantial blood collection in the subarachnoid space) who had no preexisting chronic neurological disease or

deficit and for whom outcome data and a DNA sample were available. The study sample was limited to Caucasian subjects because of differences in *HP* allele frequency by race as has been shown in previously published literature[4] and because of an insufficient number of individuals of other races in our sample to make significant statistical inferences. Utilization of all ancestral backgrounds in a study such as this, in which less than 10% of the population is non-Caucasian with variable representation of the *HP* alleles, potentially introduces bias due to inequities in allele frequencies. Given the cohort design of the study, Hardy-Weinberg equilibrium was not assessed.

Demographics and Patient Characteristics

Demographic information including age, sex, and race were recorded by the research team once the patient was enrolled in the study. A patient's medical history was abstracted from the medical record upon entry into the study as part of the original prospective study. The Hunt and Hess and Fisher grades were used to determine the severity of the aSAH. The Hunt and Hess classification (a clinical grading scale) score was abstracted from medical records based on the attending neurosurgeon's report of patient's admission examination. The World Federation of Neurosurgical Societies grades were not obtained in these in patients. The Fisher grading system,[7,10] a scale that denotes the amount and distribution of blood in the subarachnoid space demonstrated on CT scans, was used; grades were determined by the attending neurosurgeon/neuroradiologist who read the admission CT scan taken within 24 hours of hemorrhage. Of note, in clinical studies of aSAH, patients with SAH of Fisher Grades 1, 2, and 3 have an escalating degree of disability, but patients with Grade 4 SAH have a disability that falls between that of 2 and 3.[9,11] The modified Fisher scale corrects this problem but was not available for all patients in the study and could not be used. To correct for the lack of linearity, the Fisher score was recoded so that Fisher Grade 4 hemorrhages (diffuse or no subarachnoid blood with cerebral or ventricular blood) were given a value of 3 and Fisher Grade 3 hemorrhages (localized clot and/or vertical layers of blood) a value of 4 The Fisher grade is reported in the original form (Fisher Grade 3 = localized clot and/or vertical layers of blood).

DNA Extraction

Blood or CSF samples drawn after patient enrollment were used for DNA extraction. In a small number of individuals (1.0%) DNA was extracted from CSF rather than blood because no blood sample was available. Blood and CSF specimens were processed within 48 hours of collection. DNA was extracted from blood using a simple salting-out procedure, as described by Miller and colleagues.[16] DNA was extracted from CSF using an extraction kit (Qiagen).

Genotyping Procedure

Quantitative real-time polymerase chain reaction was used to generate genotypes and evaluate relative copy number of the *HP* α alleles. We multiplex-amplified the region containing the duplication that identifies the *HP* α alleles and multiplex-amplified a region 5′ to the *HP* gene as a control measure for relative comparisons. Quantitative real-time polymerase chain reaction was conducted using Taqman technology that ran ABI7000 and

SDS 2.0 software (Applied Biosystems Incorporated). Raw data were analyzed using the $\Delta\Delta C_T$ method.

Samples were evaluated in 2 ways: the 3 possible genotype groups (*HP α1-α1*, *HP α1-α2*, and *HP α2-α2*) were used for one analysis; in addition, we segregated subjects into *α-2* allele carriers and *α-1* allele carriers.

Outcome

Mortality status was abstracted from medical records when possible. When mortality status was unclear, the patient's attending physicians was contacted. A trained neuropsychological technician obtained Glasgow Outcome Scale (GOS) scores and modified Rankin Scale (mRS) scores at 3 months after aSAH. Assessments were completed during a face-to-face interview in the outpatient neurosurgery clinic. If the individual was unable to attend the in-person meeting, GOS and mRS scores were obtained by telephone interview with the patient or primary caregiver. The neuropsychological technician was blinded to genotyping results.

Data Analysis

Univariate analysis identified potential covariates. Multivariate logistic regression analyses were conducted to determine the effects of genotype on outcome while controlling for covariates identified in univariate analysis. An α level of 0.05 was considered significant for all analyses.

Results

This sample of 193 Caucasian patients was primarily female (n = 138 [71.5%]) and the mean age (± SD) was 54.45 ± 11.1 years (range 18–75 years). The severity of hemorrhage was assessed by the Fisher grade, and clinical presentation upon admission was measured using the Hunt and Hess grade (Table 1). Twenty-five individuals (13%) had the *HP α1-α1* genotype, 109 (56%) had the *HP α1-α2* genotype, and 59 (31%) had the *HP α2-α2* genotype (Table 1); 168 patients (87.0%) were *α2* allele carriers and 134 were *HP α1* carriers (Table 1), matching the distribution found in other Caucasian populations.

There were no significant differences in demographic or clinical characteristics based on genotype (comparing *HP α1-α1*, *HP α1-α2*, and *HP α2-α2* groups). *HP α2* homozygotes were older (p = 0.02) and more likely to have a Fisher grade of 3 (the worst Fisher grade) than Hp α1 carriers (p = 0.0329; Table 1). Interestingly, *HP α1* carriers more often had diabetes mellitus (chi-square test = 4.034; p = 0.05) and a history of cardiac disease (chi-square test = 4.330; p = 0.04), although not hypertension (data not shown). There were no other significant differences in demographic or clinical variables between *HP α2* homozygotes and *α1* carriers.

We found a relationship between *HP* genotype and the dichotomized mRS score; the *HP α2-α2* genotype, compared with the *HP α1-α1* genotype, was associated with worse outcome at 3 months after hemorrhage (chi-square test = 6.29; p = 0.04). This finding remained significant in multivariate analyses controlling for age, sex, Fisher grade, and Hunt and Hess grade (OR 4.138; p = 0.0463) (Table 2). We found a similar relationship for the

HP α2 allele (*HP α1-α2* or *HP α2-α2*) in that outcomes were worse at 3 months than when compared to *HP α1* homozygotes (chi-square test = 4.25; p = 0.04; data not shown), suggesting that the *α2* allele dose may contribute to the poor outcome of these patients, although significance of this relationship was lost in the multivariate model (p = 0.07). We found no significant differences in GOS score or mortality rate by *HP* genotype, *HP α1* allele presence, or *HP α2* allele presence (data not shown).

Discussion

The presence of the *HP α2-α2* genotype in patients with aSAH predicted a significantly worse outcome, measured using mRS scoring, at 3 months, after controlling for other potentially confounding variables. Interestingly, patients with at least one *HP α2* allele were older and were more likely to have a Fisher grade of 3. We did not find the same results when exploring genotypic effects in relation to the GOS score. The lack of significance may be due to the increase in categories available with the mRS, allowing for assessment of more refined recovery and the detection of smaller differences.

In our sample of Caucasians, 87% were carriers of the *HP α-2* allele, similar to the distribution found in other Caucasian populations.[2,3,12] In our sample, carriers of the *HP α2* allele had worse 3-month outcomes compared to those without the *HP α-2* allele (*HP α1-α1* genotype), as measured by the mRS after aSAH, similar to the findings of the 1 other study on this topic that had a smaller sample size.[3] The Hp α2 isoform is associated with a weaker affinity for Hgb, possibly contributing to a decreased ability to inhibit free radical production and oxidative stress, which may negatively impact recovery.[3] The α-2 isoform's decreased Hgb binding may lead to poorer CSF clearance in Hp α-2 carriers. Animal studies involving experimental SAH have shown that mice genetically modified to contain the *HP α2-α2* genotype develop increased leukocyte inflammation and more severe cerebral vasospasm than wild-type animals with the *HP α1-α1* genotype, suggesting a direct role of the *HP α2-α2* genotype with more severe aSAH sequelae.[5] Additional work in these genetically modified *HP α2-α2* mice has demonstrated that vasospasm may be prevented through the administration of an exogenous nitric oxide donor[17] or a glutathione peroxidase mimetic.[9] The role of Hp in response to aSAH is unclear; however, the genetic variation driving altered protein production and/or function is likely important for clearance of Hgb, free radical neutralization, and containing inflammation. It appears that the *HP α2* gene results in protein isoforms that do not function as well in these abilities and may lead to decreased amounts of Hp protein available to carry out these functions, both of which increase risk for worse recovery from aSAH.

In our study sample, the patients who carried the *α-2* allele were older than those who did not carry the allele. It is unknown why this increase in frequency was present in our patient population; however, it may be possible that, due to the *HP α-1* allele's associations with other diseases such as infection, coronary artery disease, and liver disease, *α-1* allele carriers may have accelerated physiological processes that are associated with earlier presentation with aSAH. Although the increased age of the *α-2* allele carriers may contribute to poor outcomes after aSAH, our multivariate analysis suggested this may not to be the case.

Limitations

This project used DNA samples and data collected as part of a prospective, descriptive study. Genotyping and analyses were performed prospectively and the data collected prospectively, but some data were extracted upon study enrollment from medical records of that admission. In particular, Fisher grade and Hunt and Hess grade were extracted from the medical records, and this may have introduced some inadvertent bias. Data are collected as soon after study enrollment as possible, generally within 24 hours of admission, and any questionable data are discussed. The investigative team includes a neurosurgeon providing care for these patients, who assigned many of these scores and reviewed others. It is possible that scores were incorrectly assigned, and this could have altered our results.

We did not include cerebral vasospasm, delayed cerebral ischemia, or other secondary injuries in our analyses. It may be that the *HP* genotype modifies cerebral vasospasm or the occurrence of delayed cerebral ischemia, driving the relationship between *HP* genotype and outcome after aSAH. Research to explore the relationship between *HP* genotype's and Hp isoform's specific contributions to cerebral vasospasm and delayed cerebral ischemia is ongoing and should provide clarification of this relationship and the mechanism driving our findings of variable outcome in patients with different *HP* genotypes.

Due to the differences in allele frequency distribution among African Americans and Asians/Pacific Islanders, as well as the limited racial representation in our patient population, we were unable to evaluate the relationship between *HP* genotype and functional outcomes among these races. Future research will analyze the associations between *HP* genotype in these races in hopes of determining whether certain populations suffer from increased morbidity after aSAH related to the frequency of the *α-2* allele.

Conclusions

This study examined the relationship between *HP* genotype and functional outcome (GOS score, mRS score, and mortality) after aSAH. The finding of a relationship between *HP α-2* allele presence and the 3-month mRS score suggests that genetic influences play a role in the morbidity of aSAH. This is one of the largest cohorts of aSAH patients in whom a specific genetic polymorphism has been found to predict outcome, although translation is hampered by lack of understanding of the mechanism through which the *HP α-2* allele affects outcome. While the relationship between *HP* genotype, Fisher grade, and recovery from aSAH is complex, the finding of a *HP α-2*/mRS score relationship, along with preclinical animal work, will open up a new field of research to understand the effects of systemic proteins in this brain disease. Additional work with larger sample sizes controlling for additional clinical factors, such as cerebral vasospasm and delayed cerebral ischemia, are needed to clarify the role of *HP* genotype in recovery from aSAH.

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Abbreviations used in this paper

aSAH	aneurysmal subarachnoid hemorrhage
GOS	Glasgow Outcome Scale
Hgb	hemoglobin
Hp	haptoglobin
mRS	modified Rankin Scale

Table 1

Demographic and clinical variables of 193 patients stratified by *HP* genotype*

Variable	All Patients	*HP α1-α1*	*HP α1-α2*	*HP α2-α2*	*HP α1+*	*HP α1−*
no. (%)	193	25 (13)	109 (56)	59 (31)	134 (69)	59 (31)
mean age (± SD)	54.5 ± 11	53.0 ± 11	53.3 ± 11	57.3 ± 11†	53.2 ± 11†	57.3 ± 11†
female sex (%)	138 (71)	17 (68)	78 (72)	43 (73)	95 (71)	43 (73)
mean Fisher grade/mode	2.94/3	2.86/2 & 3	2.87/3	3.08/3	2.84/3‡	3.07/3‡
mean H&H grade/mode	2.68/3	2.48/2 & 3	2.68/3	2.76/2 & 3	2.63/3	2.75/2 & 3
no. w/ hypertension (%)	69 (36)	11 (44)	35 (32)	23 (39)	46 (34)	23 (39)
no. w/ other cardiac history (%)	20 (10)	2 (8)	8 (7)	10 (17)	10 (7)§	10 (17)
no. w/ neurological history (%)	14 (7)	2 (8)	7 (6)	5 (9)	9 (7)	5 (9)
no. w/ diabetes mellitus (%)	9 (4.6)	1 (4)	8 (7)	0 (0)	9 (6.7)¶	0 (0)
no. w/ pst aneurysm site (%)	66 (24)	9 (36)	38 (34)	19 (32)	47 (35)	19 (32)
no. w/ coil Tx (not clipped) (%)	115 (60)	16 (64)	64 (59)	35 (59)	80 (60)	35 (59)

** HP 1+ = HP α1-α1* and *HP α1-α2; HP 1− = HP α2-α2;* H&H = Hunt and Hess; pst = posterior; Tx = treatment.

† p = 0.02.

‡ p = 0.0329, chi-square test = 6.829.

§ p = 0.037, chi-square = 4.3.

¶ p = 0.045, chi-square = 4.035.

Table 2

Multivariate logistic regression results for 3-month mRS score and *HP* genotype*

	3-Mo mRS Score & Genotype		
Variable	**OR**	**95% CI**	**p Value**
age	1.003	0.97–1.037	0.8424
sex (vs female)	1.049	0.483–2.281	0.9035
Fisher Grade 2 (vs 4)	**0.134**	**0.037–0.486**	**0.0022**
Fisher Grade 3 (vs 4)	0.644	0.0282–1.475	0.2981
H&H grade (1–2 vs 3–5)	**0.349**	**0.161–0.755**	**0.0075**
HP a1-a2 genotype *(a1-a1)*	2.977	0.767–11.557	0.1149
HP a2-a2 genotype *(a1-a1)*	**4.138**	**1.024–16.733**	**0.0463**

* Boldface values indicate significance ($p < 0.05$).