Journal of Medicine in Scientific Research

Volume 2 | Issue 3 Article 9

Subject Area:

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Recommended Citation

Ateya, Ahmed M.; El-Bassiouny, Ahmed A.; El-Garwany, Islam; Gobbah, Khaled; Ibrahim, Mahmoud H.; Fahmy, Nagia A.; and El-Nabi, Sobhy H. (2019) "Haptoglobin genotyping and risk of cerebral vasospasm after aneurysmal subarachnoid hemorrhage," *Journal of Medicine in Scientific Research*: Vol. 2: Iss. 3, Article 9.
DOI: https://doi.org/10.4103/JMISR.JMISR_43_19

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Original Article

Haptoglobin genotyping and risk of cerebral vasospasm after aneurysmal subarachnoid hemorrhage

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Abstract

Background

Aneurysmal subarach noid hemorrhage (aSAH) represents roughly 6–8% of all stroke types. Almost 70% of patients develop angiographic vasospasm, and 30% of them will have delayed cerebral ischemia (DCI). An 'omic signature' could combine genetic, proteomic, and metabolomic phenotypes into an accurate predictive model. Haptoglobin (Hp) genotypes could be used to stratify risk of resulting cerebral vasospasm (CV) and DCI, to give prognostic data dependent on distributed result probabilities, and to develop novel medications dependent on individual pathophysiological models.

Objective

This research intends to investigate the clinical and radiological factors as indicators for risk of development of CV after aSAH in Egyptian population, with the review of Hp genotype role as a predictor for CV.

Patients and methods

A total of 50 patients with aSAH were enrolled and followed up clinically and radiologically by transcranial Doppler examination for 14 days following presentation to early recognize hemodynamic changes related with CV and additional events of DCI as a result of CV. In this investigation, we attempted to analyze clinical data to find the potential hazard factors that are prescient of CV and DCI during the acute phase of aSAH.

Results

Approximately 34 (68%) patients developed CV; among them, 19 (38%) patients had DCI. History of hypertension [relative risk (RR)=1.6], diabetes mellitus (RR=1.5), and smoking (RR=1.5) had a significant independent relationship (P<0.05) with short-term hazard to develop CV following aSAH. However, age, sex, dyslipidemia, cardiovascular disease, and peripheral vascular disease did not show any relationship. Regarding poor Fisher scale and poor Hunt and Hess score, both demonstrated significant relationship with CV (P<0.05).

Conclusion

Hypertension, diabetes, smoking, poor Fisher grade, and poor Hunt and Hess scale are independent risk factors for CV. The Hp genotype may be used as a predictor for risk for development of CV after aSAH. This has the potential for use in risk stratification.

Keywords: Haptoglobin, subarachnoid hemorrhage, vasospasm

Introduction

In a deliberate review of populace-based investigations, the frequency of aneurysmal subarachnoid drain (aSAH) ranged from 2 to 16 for every 100 000 populace. In that review, the pooled age-balanced frequency rate of aSAH in low-to medium salary nations was observed to be practically twofold that of high-income nations [1].

Access this article online

Quick Response Code:

Website: www.jmsr.eg.net

DOI: 10.4103/JMISR.JMISR_43_19

aSAH is related with a more noteworthy 35% mortality along the initial 3 months. Delayed cerebral ischemia (DCI) because

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How to cite this article: Ateya AM, El-Bassiouny AA, El-Nabi SH, Fahmy NA, Ibrahim MH, El-Garwany I, Gobbah K. Haptoglobin genotyping and risk of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. J Med Sci Res 2019;2:224-9.

of cerebral vasospasm (CV) occurs in ~33% of all patients and accounts for more than 20% of its general morbidity and mortality (Vini *et al*., 1997).

Vasospasm is the narrowing of the major cerebral vessels following aSAH and is a main cause of the morbidity and mortality related to aSAH. Approximately 67% of patients with SAH will develop CV [2].

Weir *et al*.[3] discovered that CV has a biphasic course, with an acute and chronic stage. The acute stage normally starts 3–4 h after hemorrhage, with quick and spontaneous resolution. Conversely, the chronic stage starts 3–5 days later, with greatest narrowing between days 6 and 8, which resolves around 14 days after presentation.

Vasospasm can be detected angiographically or clinically. Radiologic modalities used to detect CV include computed tomography angiography, magnetic resonant angiography, transcranial Doppler (TCD), and catheter angiography [4].

Despite the fact that there are numerous speculations on the pathogenesis of CV, it still remains an inadequately understood issue. Zucker[5] noticed that lysed erythrocytes prompted smooth muscle constriction of cerebral arteries in warm blooded animals.

New advances in molecular genetics have uncovered a few genes whose products hypothetically mediate CV and genetic polymorphisms that predict CV risk as well as poor prognosis. Understanding the genetic factors of a disease may give knowledge into novel helpful directions regarding development of treatment modalities [2].

Haptoglobin (Hp) is a serum protein delivered basically by hepatocytes that bound to free hemoglobin from lysed erythrocytes. The bound complex is taken up by macrophages through the CD163 receptor, probably decreasing extracorpuscular hemoglobin toxicity [6].

The Hp gene is found on human chromosome 16q22. It exists in two alleles, and three genotypes are conceivable: Hp 1-1, Hp 1-2, or Hp 2-2. The Hp 1-1 item is a linear dimer, the Hp 2-1 item is a linear polymer, and the Hp 2-2 item is a cyclical polymer [7].

These structural differences present distinctive restricting affinities, with more prominent binding and clearing of hemoglobin in Hp 1-1 people in contrast to Hp 2-2 people. Accordingly, the Hp 2-2 allele is believed to be more proinflammatory than the Hp 1-1 allele, prompting significant reaction, invulnerable oxidation, and vasoconstriction [8].

Genetic risk stratification for CV holds great potential. Close relatives of patients with aneurysms might be screened for their own risk for aneurysm development and rupture. Genomic biomarkers may likewise be utilized to stratify patients with SAH for stepwise medical care as indicated by vasospasm risk, in addition to drug administration [2].

Aims and objectives of the study

This investigation was meant to examine the clinical and radiological risk factors as an indicator for CV after aSAH in Egyptian populace. This permits hazard factor stratification of patients with aSAH who are at higher risk for CV.

Patients and methods

Study sample

Ethical approval and consent was taken. Fifty patients with acute aSAH (e.g. with history ≤48 h), admitted in Matareya Teaching Hospital, were selected during the period from November 2016 till June 2018 for this planned case–control study on the basis of the accompanying criteria.

Inclusion criteria

Adult patients (ages 30–65 years) of both sexes, diagnosed with acute aSAH confirmed by computed tomography (CT) scan and digital subtraction angiography, were included.

Exclusion criteria

The following were the exclusion criteria:

(1) Patients with a prior neurological insult owing to previous history of stroke
(2) Patients with poor temporal TCD window required for bedside evaluation of CV
(3) Organ failure or any systemic illness could influence the cerebral circulation, for example, hepatic, cardiovascular, or renal end-organ failure
(4) Patients with history suggestive of aSAH owing to dissecting or mycotic aneurysm.

Measures

Demographic and medical risk factors

All patients with acute aSAH were surveyed for risk factors for SAH with respect to clinical data such as age, sex, hypertension (HTN), diabetes mellitus (DM), dyslipidemia, smoking (SMK), cardiovascular disease, and peripheral vascular disease (PVD). The age variable was dichotomized into more than or equal to 52 years and less than 52 years (the mean age was selected as the cutoff value).

Grading scales

The initial severity of aSAH was determined on admission by use of clinical Hunt and Hess and radiological Fisher's grading scales. The Hunt–Hess and Fisher grades on admission were dichotomized into good-grade status (Fisher grades 1 and 2 or Hunt–Hess grades 1–3) and poor-grade status (Fisher grades 3 and 4 or Hunt–Hess grades 4 and 5).

Intracranial vasospasm

TCD examination was performed using DWL® - EZ-Dop® machine -Compumedics Germany GmbH, Singen, Germany. TCD utilizes low-frequency pulsed insonation (2 MHz) to measure blood flow velocity within proximal cerebral arteries, obtaining systolic and diastolic peaks and mean flow velocities (MFV). The latter is defined as (systolic + diastolic)/3 + diastolic velocities, according to Alexandrov *et al.* [9].

All patients received initial TCD examination (day 1) after admission serving as a baseline state for cerebral circulation. Follow-up TCD examinations was done at fixed intervals (days 3 and 10) after the onset of aSAH.

TCD examination protocol for intracranial arteries was performed according to Alexandrov *et al.* [9]. Artery-specific thresholds for detecting vasospasm were used according to established criteria by Lysakowski *et al.* [10]. The following threshold flow velocities were used to indicate CV: MCA MFV more than 120 cm/s, ACA MFV more than 130 cm/s, PCA MFV more than 110 cm/s, ICA MFV more than 130 cm/s, VA MFV more than 80 cm/s, and BA MFV more than 95 cm/s. Flow velocities above the predefined threshold are indicative of suspect diagnosis of CV. A positive TCD test result for CV is confirmed by two consecutive measures of increased flow velocities of suspected artery.

Clinical deterioration from delayed cerebral ischemia

Symptomatic vasospasm was characterized as generally unexplained (a) clinical deterioration (i.e. new focal deficit, decline in conscious level, or both) or (b) another infarct on CT that was not noticeable on the admission or postoperative immediate scan, or both.

Patients associated with DCI auxiliary to vasospasm (affirmed with TCD examination) were physically inspected, have urgent CT output, and laboratory examination to discount other potential reasons for clinical deterioration, for example, hydrocephalus, rebleeding, cerebral edema, metabolic disturbances, and seizures, which were thoroughly excluded. Clinical deterioration, thought to be steady with vasospasm, was treated according current guidelines.

Hypodensities on CT imaging resulting as a complication of endovascular coiling, ventricular catheter, or intraparenchymal hematoma ought not be viewed as cerebral areas of dead tissue from DCI.

Statistical analysis

Statistical package for the social sciences (SPSS) IBM Corp. Released 2010, IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp, USA. Differences in demographics, clinical, and radiological grading scales and TCD findings based on CV status and genotypes were investigated using χ^2 for categorical variables. The differences were considered significant at P value ($P \leq 0.05$). Risk estimation was used to evaluate the relationship between investigated variables and occurrence of CV.

Results

Patients' demographics and risk factors

Fifty patients with affirmed acute aSAH were clinically and radiologically distinguished and enrolled for our examination. Patients were followed up intently for 14 days after presentation to early distinguish manifestations and indications of CV and DCI.

At the end of follow-up, patients were assembled by event of CV either radiologically or symptomatic. Thirty-four (68%, group A) patients created CV, whereas the rest of the 16 (32%, group B) patients did not hint at any either radiological or symptomatic CV.

Table 1 shows the distribution of potential risk factors among study patients. The statistics results showed independent significant effect between occurrence of CV and HTN, diabetes, and SMK ($P < 0.05$). The risk estimates of probability to develop CV in relation to potential risk factors showed a higher risk with HTN [relative risk (RR)=1.6; odds ratio (OR = 4)], diabetes (RR = 1.5; OR = 3.4), and SMK (RR = 1.5; OR = 3.6). Thus, individuals who are hypertensive, diabetic, or smokers are at higher risk with higher risk to develop CV after aSAH than other patients who are not.

Other factors, for example, age, sex, hyperlipidemia, history of cardiovascular disease, or history of PVD, did not reach a significant distribution among our patients, meaning that they have no significant relationship with developing CV among study patients.

Clinical and radiological predictors of vasospasm

Using Hunt and Hess scale (as a clinical predictor) and Fisher grade (as a radiological predictor) for developing CV after aSAH, patients of this study were classified according their grade into having either poor versus good grade. Distribution of both grades among study groups of patients was statistically investigated (Table 2).

According to this distribution, both Hunt and Hess and Fisher grades achieved a statistically significant differences among the whole study population ($P < 0.05$). So, patients with CV after aSAH tended to acquire a poorer grade of both scales. It was also noted that among the study patients with CV, Fisher grade had a higher significance with up to 85% of patients having poor grade among those who developed CV.

Overview on patients' outcome

Follow-up status was determined for the patients of this study for 14 days after the index event. Nineteen (38%) patients had DCI versus 31 (62%) patients who did not develop DCI. Table 3 shows the distribution of CV detected by TCD during follow-up among patients in relation to developing DCI. TCD vasospasm did not reach significant relationship with developing DCI.

Discussion

aSAH represents roughly 6–8% of all stroke cases, and 22–25% of cerebrovascular deaths. Approximately 70% of patients develop angiographic vasospasm, and 30% of them will had DCI. DCI is a common complication in patients who have aSAH, and it is the most critical reason for morbidity and mortality in such patients [11].

Vasospasm after aSAH is a complex event made out of reversible vasoconstriction, combined with disruption of normal cerebral vascular autoregulation, prompting a decrease of cerebral blood flow. Proximal vessels at the base of the

Table 1: Study patients demographics and risk factors for cerebral vasospasm distribution

Risk	Group A, (*n*=34) [*n* (%)]	Group B, (*n*=16) [*n* (%)]	RR	OR	*P*
Age (years)					
<52	18 (52.9)	6 (37.5)	1.2	1.8	0.31
>52	16 (47.1)	10 (62.5)			
Sex					
Male	16 (47.1)	5 (31.3)	1.2	1.9	0.29
Female	18 (52.9)	11 (68.8)			
HTN	24 (70.6)	6 (37.5)	1.6	4	0.03*
DM	23 (67.6)	6 (37.5)	1.5	3.4	0.04*
DLP	21 (61.8)	11 (68.8)	0.9	0.7	0.6
SMK	21 (61.8)	5 (31.3)	1.5	3.6	0.04*
CVD	6 (17.6)	3 (18.8)	0.9	0.9	0.93
PVD	6 (17.6)	2 (12.5)	1.1	1.5	0.64

CVD, cardiovascular disease; DLP, dyslipidemia; DM, diabetes mellitus; HTN, hypertension; OR, odds ratio; PVD, peripheral vascular disease; RR, relative risk; SMK, smoking; TCD Vs, transcranial Doppler vasospasm. *Statistically significant relation (P<0.05).

Table 2: Clinical and radiological predictors of cerebral vasospasm distribution among the study patients

Risk	Group A, (*n*=34) [*n* (%)]	Group B, (*n*=16) [*n* (%)]	RR	OR	*P*
Poor Hunt and Hess scale	21 (61.8)	5 (31.3)	1.5	3.6	0.04*
Poor Fisher scale	29 (85.3)	9 (56.3)	1.8	4.5	0.03*

OR, odds ratio; RR, relative risk. *Statistically significant relation (P<0.05).

Table 3: Distribution of cerebral vasospasm as risk factor for delayed cerebral ischemia among the studied patients

Risk	Group C (*n*=19) [*n* (%)]	Group D (*n*=31) [*n* (%)]	*P*
Cerebral vasospasm			
Yes	14 (73.7)	20 (64.5)	0.5
No	5 (26.3)	11 (35.5)	

cerebrum are specially influenced by CV; anyways distal vessel vasospasm may likewise cause impaired autoregulation and lead to promote alteration of blood flow [12].

In this study, a group of 50 patients with aSAH were prospectively examined and followed up clinically and by TCD examination for early detection of signs and symptoms of CV.

During follow-up of our study patients, the early detection of CV by TCD was confirmed in 68% of our study cohort along a follow-up period of 14 days after onset of aSAH. This is in congruency with previously reported studies using TCD in diagnosis of CV in patients with aSAH [13].

Regarding nonmodifiable risk factors, both age and sex did not reach significant relationship with risk of CV development after aSAH. This is in consistency with studies by Magge *et al.*[14] and Yin *et al.* [15], who reported negative relationship between age and risk of CV.

Although the incidence of CV in our studied patients is greater in younger patients, with age below 52 years (52.9%, n = 18) in comparison with those with age more than 52 years (47.1%, n = 16); this did not reach significant relation.

Preexisting systemic HTN was associated with worse outcome after SAH and with cerebral infarction, as reported by Ohman *et al.* [16]. In our study cohorts, patients developing CV after aSAH tended to have a history of HTN with significant independent relationship (70 vs. 30%). Moreover, preexisting HTN increases the risk for development of CV by 1.6 times higher than nonhypertensive patients. This is consistent with findings from Inagawa *et al.*[17] who reported that history of HTN was associated with CV after aSAH.

DM, according to our results, appears to be an independent predictor of CV after aSAH. Among patients with CV, diabetes achieved a significant distribution (P < 0.05) with nearly 67% (n = 23) of patients having diabetes. Moreover, DM increased the risk for development of CV by 1.5 fold greater than nondiabetic.

In a study conducted by Dumont *et al.* [11], it was reported that preexisting DM was independently correlated with CV, despite adequate glycemic control after SAH, and speculated that the long-standing effects of DM were more relevant to the development of CV, rather than acute postictal hyperglycemia.

Exploring our study results, SMK was distributed significantly among our patients, where smokers were at higher risk for development of CV than who do not (nearly 62 vs. 38%). This is in consistency with de Rooij *et al.*[18] who found that SMK was strongly independently associated with an increased risk of CV.

Other analyzed risk factors, for example, dyslipidemia, history of coronary vascular disease, and PVD, were distributed equally among the study population without any significant distribution (P > 0.05) or relation to occurrence of CV after aSAH. Our results are congruent with results of recent systematic review investigating risk factors for CV following aSAH [19].

Regarding clinical grade, using Hunt–Hess clinical grading scale, patients who developed CV following aSAH tended to have a poorer initial grade (61.8%) compared with those with good grade (38.2%), achieving significant relationship (P < 0.05). This is similar to conclusions reported by Moskowitz *et al.*[20] and Ryttlefors *et al.* [21], who reported positive associations between Hunt–Hess grade and CV defined by clinical and radiological criteria.

Reviewing our study results, Fisher grade achieved a significant distribution among our patients where those who developed CV tended to have poorer initial grade (>85%, n = 29, P < 0.05) in comparison with those with good initial grade. Those results are in keeping with the majority of prior reports confirming that

there is undoubtedly a strict correlation between the amount of subarachnoid blood detected by CT scan soon after SAH and the subsequent development of CV [19].

A previous study of 219 Egyptian blood donors[22] revealed a remarkably low prevalence of Hp 1-1 (4.1%) and a corresponding low Hp 1 gene frequency 0.21. These figures are the lowest ever reported from the Middle East or the Mediterranean countries. However, in a later study[23] investigating Hp polymorphism frequency among 505 healthy Egyptian individuals, the distribution was nearly the same as we have in our study results.

Borsody *et al.*[24] examined the genotyping of Hp as a predictor of CV. The authors guessed that phenotypes of Hp with more affinity extracorpuscular hemoglobin could lower the effects of extracorpuscular hemoglobin which prompt vasospasm. Once in the subarachnoid space, inflammatory cells, macrophages, and neutrophils phagocytize the extravasated, degrading red blood cells. This procedure happens to clear free hemoglobin and promote neurostability and recovery. Hemoglobin removal is facilitated by combining of hemoglobin with Hp for fast engulfment by resistant cells [25].

Later, Budohoski *et al.*[26] guessed that CV following aSAH could include oxyhemoglobin release, inflammatory reaction, diminished nitric oxide levels, and an increased expression of endothelin-1.

With respect to recently referenced information, assurance of genetic factors for CV following aSAH may add to ability to exact distinguishing of patients at high risk of poor outcome.

The occurrence of CV as predictors for short-term risk for the development of DCI following aSAH in our study cohorts was investigated. DCI was detected in 19 of 50 (38%) patients which is in accordance with recent published data in the literature [27]. CV-induced DCI occurred in 14 of 50 (28%) patients with aSAH in this study. χ^2 test of independence presuming CV as a predictor for DCI did not show a significant association ($P > 0.05$) [Table 3].

In recent years, the relation between CV and DCI is being questioned increasingly. First, the peak incidence of angiographic vasospasm during the second week after SAH is ~70%, but the incidence of clinically detected DCI is only around 30% [4].

Extra proof regarding a distinction between vasospasm and clinical result gets from investigation of the calcium channel blocker, nimodipine. This agent is the main affirmed medication that diminishes the occurrence of poor outcome after aSAH, and an orderly survey demonstrates that nimodipine lessens the danger of poor outcome without any clear effect on vasospasm itself [28]. Furthermore, results from randomized, placebo-controlled trial of clazosentan administration conducted by Macdonald *et al.* [29], the CONSCIOUS-1 trial, provide further evidence of a disconnect between angiographic vasospasm and DCI.

Conclusion

In conclusion, CV and DCI are important neurological complication of aSAH. The development of CV after aSAH is multifactorial and may involve several distinct but interconnected pathological processes. Based on these processes, multiple biomarkers have been proposed to be used as predictors of CV after aSAH. HTN, DM, and SMK are the most independent significant factors to predict CV following aSAH.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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