



بسم الله الرحمن الرحيم

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ملاحظات: لا يوجد



**HAPTOGLOBIN GENOTYPING AND RISK OF  
CEREBRAL VASOSPASM AFTER  
ANEURYSMAL SUBARACHNOID  
HEMORRHAGE**

*Thesis*

*Submitted for Partial Fulfillment of M.D. Degree  
In Neurology*

*By*

**Ahmed Mohammed Ali Ateya**  
*MSc. Neuropsychiatry*

*Supervisors*

**Prof. Dr. Mahmoud Haroon Ibrahim**  
*Professor of Neurology- Faculty of Medicine- Ain Shams University*

**Prof. Dr. Nagia Aly Fahmy**  
*Prof. of Neurology, Faculty of Medicine - Ain Shams University*

**Prof. Dr. Sobhy Hassab El-Nabi**  
*Prof. of Genetics and Molecular Biology,  
Faculty of Science - Menoufia University*

**Prof. Dr. Ahmed Ali El-Bassiouny**  
*Prof. of Neurology, Faculty of Medicine - Ain Shams University*

**Faculty of Medicine  
Ain Shams University  
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# Contents

Title	Page No.
Acknowledgment.....	i
Dedication.....	iii
List of Abbreviations.....	iv
List of Figures .....	vii
List of Tables .....	ix
Introduction .....	1
Aims and Objectives of the Study.....	5
Review of Literature.....	
- <b>Chapter (1):</b> Outcome of aneurysmal subarachnoid hemorrhage .....	6
- <b>Chapter (2):</b> Pathophysiology of cerebral vasospasm .....	17
- <b>Chapter (3):</b> Genomics of cerebral vasospasm... ..	27
- <b>Chapter (4):</b> Biological and clinical significance of haptoglobin .....	41
Patients and Methods.....	64
Results .....	75
Discussion.....	100
Summary.....	116
Conclusion .....	121
Recommendations .....	123
References .....	125
Arabic Summary.....	-

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# **DEDICATION**

This work is dedicated to my parents, my wife and my daughters; whose love, praying, caring and sacrifices enlighten me through this research work.

## List of Abbreviations

Abb.	Full term
<b>AA</b>	: Arachidonic acid
<b>aCV</b>	: Angiographic cerebral vasospasm
<b>AD</b>	: Alzheimer's disease
<b>ApoE</b>	: Apolipoprotein E
<b>aSAH</b>	: Aneurysmal subarachnoid hemorrhage
<b>BBB</b>	: Blood brain barrier
<b>CAMs</b>	: Cell adhesion molecules
<b>CBS</b>	: Cystathionine $\beta$ -synthase
<b>CGRP</b>	: Calcitonin-gene related peptide
<b>CICR</b>	: Calcium induced calcium release
<b>CO</b>	: Carbon monoxide
<b>COX</b>	: Cyclooxygenase
<b>CT</b>	: Computed tomography
<b>CTA</b>	: Computed tomography angiography
<b>CV</b>	: Cerebral vasospasm
<b>CVD</b>	: Cardiovascular disease
<b>DAG</b>	: Diacyl glycerol
<b>DCI</b>	: Delayed cerebral ischemia
<b>DLP</b>	: Dyslipidemia
<b>DM</b>	: Diabetes mellitus
<b>DNDs</b>	: Delayed neurological deficits
<b>DSA</b>	: Digital subtraction angiography
<b>EDRF</b>	: Endothelium-derived relaxing factor
<b>eNOS</b>	: Endothelial nitric oxide synthase
<b>ET</b>	: Endothelins
<b>GOS</b>	: Glasgow outcome scale
<b>H2S</b>	: Hydrogen disulfide

<b>Abb.</b>	<b>Full term</b>
<b>HO-1</b>	: Heme oxygenase-1
<b>Hb</b>	: Haemoglobin
<b>HDL</b>	: High density lipoproteins
<b>Hp</b>	: Haptoglobin
<b>Hp-Hb</b>	: Haptoglobin-haemoglobin
<b>HTN</b>	: Hypertension
<b>IL</b>	: Interleukins
<b>IP<sub>3</sub></b>	: Inositol triphosphate
<b>LCAT</b>	: Lecithin cholesterol acyl-transferase
<b>LDL</b>	: Low-density lipoproteins
<b>MFV</b>	: Mean flow velocities
<b>MLCK</b>	: Myosin light chain kinase
<b>MMM</b>	: Multimodal monitoring
<b>MRA</b>	: Magnetic resonance angiography
<b>MS</b>	: Multiple sclerosis
<b>NO</b>	: Nitric oxide
<b>O<sub>2</sub><sup>-</sup></b>	: Superoxide
<b>OH<sup>-</sup></b>	: Hydroxyl
<b>OxyHb</b>	: Oxyhemoglobin
<b>PAI-1</b>	: Plasminogen activator inhibitor-1
<b>PG</b>	: Prostaglandins
<b>PIP<sub>2</sub></b>	: phosphatidylinositol biphosphate
<b>PVD</b>	: Peripheral vascular disease
<b>ROS</b>	: Reactive oxygen species
<b>RyRs</b>	: Ryanodine receptors
<b>sCV</b>	: Symptomatic cerebral vasospasm
<b>SOD</b>	: Superoxide dismutase
<b>TBI</b>	: Traumatic brain injury



<b>Abb.</b>	<b>Full term</b>
<b>TCD</b>	: Transcranial doppler
<b>tPA</b>	: Tissue-type plasminogen activator
<b>TXA2</b>	: Thromboxane
<b>uPA</b>	: Urokinase plasminogen activator
<b>VLDLs</b>	: Very low-density lipoproteins

## List of Figures

Fig. No.	Title	Page No.
<b>Figure (1):</b>	Oxyhemoglobin's role in cerebral vasospasm.	<b>21</b>
<b>Figure (2):</b>	Role of free radicals after SAH.....	<b>22</b>
<b>Figure (3):</b>	A schematic diagram of the genetic structure of the Haptoglobin alleles.....	<b>42</b>
<b>Figure (4):</b>	Transcranial Doppler machine.....	<b>68</b>
<b>Figure (5):</b>	PCR thermocycler; Biometra T-personal™...	<b>71</b>
<b>Figure (6):</b>	Typical PCR gel electrophoresis patterns for different Hp genotypes.....	<b>72</b>
<b>Figure (7):</b>	Thermo Scientific O'GeneRuler 1 kb Plus DNA Ladder.....	<b>72</b>
<b>Figure (8):</b>	Study patients demographics & risk factors for cerebral vasospasm distribution.....	<b>77</b>
<b>Figure (9):</b>	Clinical & radiological predictors of cerebral vasospasm distribution among sturdy patients	<b>78</b>
<b>Figure (10):</b>	Intracranial aneurysm angioarchitecture criteria distribution among studied patients...	<b>79</b>
<b>Figure (11):</b>	Gel electrophoresis of some DNA samples of study patients showing different HP genotypes.	<b>81</b>
<b>Figure (12):</b>	Geographical distribution of Hp genotyping for studied patients over Egyptian governorates....	<b>82</b>
<b>Figure (13):</b>	Hp genotype distribution in relation to CV among studied patients.....	<b>83</b>
<b>Figure (14):</b>	Risk estimation between Hp allele & development of CV.....	<b>84</b>

## List of Figures (Cont..)

Fig. No.	Title	Page No.
<b>Figure (15):</b>	Distribution of Cerebral vasospasm & Hp genotype as risk factors for delayed cerebral ischemia among studied patients.....	<b>87</b>
<b>Figure (16):</b>	Binary regression model predicting cerebral vasospasm in relation to risk factors.....	<b>90</b>
<b>Figure (17):</b>	Case 1 presentation.....	<b>93</b>
<b>Figure (18):</b>	Case 2 presentation.....	<b>95</b>
<b>Figure (19):</b>	Case 3 presentation.....	<b>99</b>

# List of Tables

Table No.	Title	Page No.
<b>Table (1):</b>	Hunt & Hess Scale and Fisher scale.....	<b>66</b>
<b>Table (2):</b>	Study patients' demographics & risk factors for cerebral vasospasm distribution.....	<b>76</b>
<b>Table (3):</b>	Clinical & radiological predictors of cerebral vasospasm distribution among study patients...	<b>78</b>
<b>Table (4):</b>	Intracranial aneurysm angioarchitecture criteria distribution among study patients.....	<b>79</b>
<b>Table (6):</b>	Hp genotype distribution in relation to CV among studied patients.....	<b>83</b>
<b>Table (7):</b>	Risk estimation between Hp allele & development of CV.....	<b>84</b>
<b>Table (8):</b>	Distribution of different Hp genotypes in relation to clinical & radiological risk factors among studied patients.....	<b>86</b>
<b>Table (9):</b>	Distribution of Cerebral vasospasm & Hp genotype as risk factors for delayed cerebral ischemia.....	<b>87</b>
<b>Table (10):</b>	Binary regression model predicting cerebral vasospasm in relation to risk factors.....	<b>90</b>

# Haptoglobin genotyping and risk of cerebral vasospasm after aneurysmal subarachnoid hemorrhage

## Abstract:

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**Background:** Aneurysmal subarachnoid hemorrhage (aSAH) accounts for approximately 6–8% of all strokes and 22–25% of cerebrovascular deaths. Nearly 70% of patients develop angiographic vasospasm, 30% of them will develop delayed cerebral ischemia (DCI). Delayed cerebral ischemia is a common and potentially devastating complication in patients who have sustained SAH and it is the most significant cause of morbidity and mortality in patients surviving aSAH long enough to reach medical care, even exceeding direct effects of the aneurysm rupture as well as rebleeding. As a theoretical model, an “omic signature” could incorporate an individual’s genetic, proteomic, and metabolomic phenotype into a powerful predictive tool. Genetic information such as haptoglobin genotypes could be used to stratify risk of subsequent CV and DCI, provide prognostic information based on published outcome probabilities, and prompt implementation of novel treatments based on individual pathophysiological models. **Objective:** This study aims to study the genetic predisposition of Haptoglobin typing as a predictor for cerebral vasospasm (CV) after acute subarachnoid hemorrhage (aSAH) in Egyptian population. **Methodology:** The study was carried out at Matariya Teaching Hospital, Cairo, Egypt. The study 50 patients with acute aSAH were prospectively recruited and followed up clinically and radiologically by TCD examination for 14 days following aneurysmal rupture to early detect hemodynamic changes associated with CV and also occurrence of DCI secondary to CV. **Results:** As part of result analyses, about 34 patients (68%) developed CV among them 19 patients (38%) developed DCI. Only history of hypertension [RR= 1.6 (OR= 4)], diabetes mellitus [RR= 1.5 (OR= 3.4)] and smoking [RR= 1.5 (OR= 3.6)] had a significant independent relationship (P <0.05) with short term risk to develop CV following aSAH. While, Age, sex, hyperlipidemia, cardiovascular disease and peripheral vascular disease, intracranial aneurysm site and size did not achieve significant association for developing CV. Regrading poor Fisher scale (P = 0.03) and poor Hunt and Hess score (P = 0.04), it showed significant association with CV. Genotyping of Hp protein among our study cohort revealed that the relative distribution of the three common haptoglobin genotypes (Hp1-1, HP2-1 & HP2-2) among Egyptian patients of aSAH is 14%, 41% and 45%, respectively; (gene proportion being 0.34 for Hp1 and 0.66 for Hp2). Furthermore; Hp 2 allele was associated with radiographic vasospasm detected by TCD among our study patients (2-2 & 2-1 Vs 1-1: RR =5.4, OR =19.8, P <0.001). Moreover, searching for relationship between CV & Hp genotype and risk for development of DCI; both variables failed to achieve significant relationship (P >0.05). **Conclusion:** the Hp genotype may determine the susceptibility to cerebral vasospasm after acute aSAH. This has the potential for use in risk stratification by allowing for the identification of those patients requiring increased vigilance due to their inherent genetic risk for developing CV. Identifying SAH patients who are at high risk for development of vasospasm would allow for the selective administration of aggressive treatments to those patients who clearly would benefit from them.

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**Keywords:** HP, aSAH, DCI, CV, DCI



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# *Introduction*

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*Aim and Objectives of  
the Study*

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