بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / سلوي محمود عقل

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات: لا يوجد

HAPTOGLOBIN GENOTYPING AND RISK OF CEREBRAL VASOSPASM AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE

Thesis

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In Neurology

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

Abb.		Full term
HO-1	:	Heme oxygenase-1
Hb	:	Haemoglobin
HDL	:	High density lipoproteins
Hp	:	Haptoglobin
Hp–Hb	:	Haptoglobin–haemoglobin
HTN	:	Hypertension
IL	:	Interleukins
IP_3	:	Inositol triphosphate
LCAT	:	Lecithin cholesterol acyl-transferase
LDL	:	Low-density lipoproteins
MFV	:	Mean flow velocities
MLCK	:	Myosin light chain kinase
MMM	:	Multimodal monitoring
MRA	:	Magnetic resonance angiography
MS	:	Multiple sclerosis
NO	:	Nitric oxide
O_2^-	:	Superoxide
OH^-	:	Hydroxyl
OxyHb	:	Oxyhemoglobin
PAI-1	:	Plasminogen activator inhibitor-1
PG	:	Prostaglandins
PIP_2	:	phosphatidylinositol biphosphate
PVD	:	Peripheral vascular disease
ROS	:	Reactive oxygen species
RyRs	:	Ryanodine receptors
sCV	:	Symptomatic cerebral vasospasm
SOD	:	Superoxide dismutase
TBI	:	Traumatic brain injury

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

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Haptoglobin genotyping and risk of cerebral vasospasm after aneurysmal subarachnoid hemorrhage

Abstract:

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-I & 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.

Keywords: HP, aSAH, DCI, CV, DCI

Introduction

Aim and Objectives of the Study