HIGH-SENSITIVITY C-REACTIVE PROTEIN, ITS GENE POLYMORPHISM AND ISCHEMIC STROKE

Thesis

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ABSTRACT

Hs-CRP (an acute phase reactant) is considered a marker of atherosclerosis. Its level is affected by both genetic and environmental factors. We aim to study its relation to ischemic stroke and whether its gene G1059C polymorphism is related to CRP level. Significantly higher hs-CRP level is found in stroke patients than in controls. No association was found between CRP gene to G1059C polymorphism and serum level of hs-CRP or ischemic stroke.

Keywords:
Stroke, hs-CRP, polymorphism

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LIST OF ABBREVIATIONS

A/G	Adenine/Guanine
ACEIs	Angiotensin-converting enzyme inhibitors
ADP	Adenosine diphosphate
APL	Antiplatelets
APP	Acute phase proteins
Asp.	Aspartate
BBB	Blood brain barrier
C/EBP	Enhancer-binding protein
C1-q	Complement-1
C-3	Complement-3
CARE	Cholesterol and recurrent events
CBC	Complete blood count
CD	Cluster of differentiation
CD40L	CD40 ligand
CE	Cardioembolic
cGMP	Cyclic guanosine monophosphate
CHD	Coronary heart diseases
CHO	Cholesterol
Cp	Ceruloplasmin
CRP	C-reactive protein
CRP-tg	CRP-transgenic
CSF	Cerebrospinal fluid
CT	Computed Tomography
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECs	Endothelial cells
eNOS	Endothelial nitric oxide synthase
E-selectin	Endothelium selectin
ESR	Erythrocyte sedimentation rate
FBS	Fasting blood sugar
G/C	Guanine/Cytosine
GOS	Glasgow Outcome Scale
G/T	Guanine/Thyamine
HDL	High-density lipoprotein cholesterol
HMG-coA	3-hydroxy-3-methylglutaryl coenzyme A
Hp	Haptoglobin
Hs-CRP	High sensitivity CRP
ICAM	Intercellular adhesion molecule

IFN	Interferon
IgM	Immunoglobulin-M
IHD	Ischemic heart disease
IL	Interleukin
LACI	Lacunar infarction
LDL	Low density lipoprotein
LOX-1	Low density lipoprotein receptor-1
LVD	Large vessel disease
MCA	Middle cerebral artery
MCP-1	Monocyte chemoattractant protein-1
MHCs	Major histocompatability complexes
MI	Myocardial infarction
MMPs	Matrix mellaoproteinases
MMSE	Mini-Mental State Examination test
MRS	Modified Rankin Scale
NCBI	National Center for Biotechnology Information
NFκB	Nuclear factor-kappa B
NIHSS	National Institute of Health Stroke Scale
NK cells	Natural killer cells
NO	Nitric oxide
OCSP	Oxfordshire Community Stroke Project Classification
oxLDL	Oxidized low-density lipoprotein
PACI	Partial anterior circulation infarction
PAI-1	Plasminogen activator inhibitor-1
PDGF	Platelet-derived growth factor
PMNL	Polymorphonuclear leukocyte
POCI	Posterior circulation infarction
PPAR	Peroxisome proliferators activated receptors
PPBS	Post-Prandial blood sugar
P-selectin	Platelets selectin
RBCs	Red blood cells
RFLP	Restriction Fragment Length Polymerase
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SAA	Serum amyloid A
SD	Standard deviation
SMCs	Smooth muscle cells
SNP	Single nucleotide polymorphisms
SPARCL	Stroke Prevention by Aggressive Reduction of Cholesterol Levels
SPSS	Statistical Package for Social Sciences
STATs	Signal transducers and activators of transcription

T/A	Thymine/adenine
TACI	Total anterior circulation infarction
TF	Tissue factor
TGF	Transforming growth factor
TGs	Triglycerides
TIAs	Transient ischemic attacks
TNF	Tumor necrosis factor
TOAST	Trial of Org 10172 in acute stroke treatment
tPA	Tissue-type plasminogen activator
Tyr	Tyrosine
TZDs	Thiazolidinediones
US FDA	United States Food and Drug Adminsitration
UTR	Untranslated regions
UV	Ultra-violet
VCAM	Vascular cell adhesion molecule
VLDL	Very low density lipoprotein
VNTR	Variable numbers of an 86-bp identical tandom repeat
vWF	von Willebrand factor
WBC	White blood cell
WHO	World Health Organization

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INTRODUCTION

Stroke was defined according to WHO as: rapidly developing clinical signs of focal disturbance of cerebral function lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin **(Report of WHO Task Force, 1989)**.

By year 2020, cerebrovascular disease is projected to become the fourth-leading burden of disease worldwide, after heart disease, depression, and motor vehicle collisions **(Michaud et al., 2001)**.

In Egypt, the incidence of stroke was found to be 2.1 per 1000. The prevalence was 5.4 per 1000. Stroke was more prevalent in males (59.5%). Cerebral ischemia constituted 78% while cerebral hemorrhage 22% of stroke. Cerebral ischemia involved middle cerebral artery (MCA) in 73.7% and capsular hemorrhage 12% of cases **(Abdulghani and Etribi, 2003)**.

Attempts at modification of traditional risk factors have not been effective in changing national stroke rates. Despite advances in acute and prophylactic therapies, rates of stroke and stroke-related deaths continue to increase. A report from the Framingham Study shows that although the annual incidence of clinical stroke decreased in since 1950, the severity of stroke has not **(Jeffrey, 2006)**.

Atherosclerosis, the most common cause of stroke, is now believed to be a disease of chronic inflammation. It typically occurs at branch points and bifurcations in large and medium-sized elastic and muscular arteries. The extracranial internal carotid artery and the

vertebral artery are the cerebral vessels most commonly affected **(Larry et al., 2001)**.

Inflammatory processes have fundamental roles in stroke in both the etiology of ischemic cerebrovascular disease and the pathophysiology of cerebral ischemia **(Perttu et al., 2003)**.

The role of inflammatory mechanisms in the pathogenesis of cerebral artery disease is based on results of studies about acute inflammatory mediators as (C-reactive protein, fibrinogin, and other cytokines) **(Claudia and Josef, 2002)**. Using a number of inflammatory biomarkers will remodel future clinical practice in the use of medication **(Thomas and DeGraba, 2004)**.

C-reactive protein (CRP) is a plasma protein that participates in the systemic response to inflammation. Its plasma concentration increases during inflammatory states, a characteristic that has long been employed for clinical purpose **(Steven et al., 2004)**.

It was discovered in Oswald Avery's Laboratory during the course of studies of patients with Streptococcus pneumoniae infection **(Tillet and Francis, 1930)**. Sera obtained from these patients, during the early and acute phase of illness, were found to contain a protein that could precipitate the "C" polysaccharide from the pneumococcal cell wall. Forty years later, **Volanakis and Kaplan** identified the specific ligand for CRP in the pneumococcal C polysaccharide as phosphocholine, part of techoic acid of the pneumococcal wall **(Volanakis and Kaplan, 1971)**. CRP can activate the classical complement pathway, stimulate phagocytosis, and bind to immunoglobulin receptors **(Steven et al., 2004)**. Furthermore, this

protein appears to play a role in the clearance of apoptotic and necrotic host cells, thus contributing to restoration of normal structure and function of injured tissues. Like other elements of immunity, CRP perhaps has not only protective, but also potentially harmful effects. Thus, CRP has been implicated in atherogenesis **(Zwaka et al., 2001)** and in the mediation of tissue damage in acute stroke **(Shani et al., 2007)**.

High sensitivity C-reactive protein (hs-CRP) measurement enables the detection of small changes of C-reactive protein within the normal range and is capable to detect low grade inflammation in the vascular system **(Rifai and Paul, 2001)**.

With the advent of high-sensitivity assays, CRP has emerged as one of the most powerful independent predictors of cardiovascular disease **(Yeh and Willerson, 2003)**. The Centers for Disease Control and Prevention and the American Heart Association issued a (class IIa) recommendation for the screening of high-sensitivity CRP as a routine part of global cardiovascular risk assessment **(Pearson et al., 2003)**.

A polymorphism in a gene, which affects the gene function (mutation in the regulatory sequences) or the gene product (mutation in the protein coding part), can teach us about the role of the gene product(s) in disease **(Kluft and de Maat, 2003)**.

Proinflammatory genetic profiles, resulting from polymorphism in genes encoding inflammatory molecules, may contribute to the development and progression of cerebrovascular diseases **(Andrea et al., 2004)**.

There is now direct evidence that CRP gene polymorphisms affect the amount of CRP produced and indirect evidence that this is inturn might have an impact on vascular diseases **(Hage and Szali, 2007)**.