Inflammatory bio-markers and cerebrovascular disease risk

A thesis Submitted for partial fulfillment of the Master Degree in Internal Medicine

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2008

ACKNOWLEDGEMENT

First thanks GOD , the most beneficent and merciful .

I wish to express my deep gratitude and respect , to ***Professor Dr. Mohammed Ibrahim Sheta, Professor of Internal medicine ,faculty of medicine , Cairo University ,*** For his close and gracious supervision with his great experience and scientific attitude .

I offer my deepest gratitude and great thanks to ***Dr Yasser Mohammed Abdelhamid , Lecturer of internal medicine , Faculty of medicine , Cairo University ,*** for dedicating so much of his precious time and effort and his kindness , honest and constant guidance throughout the performance of this work. For him , no word of thanks or gratitude are sufficient .

Special thanks are due to ***Dr. Doaa Mohammed Atef Soliman, , Lecturer of clinical and chemical pathology , Faculty of Medicine , Cairo University,*** for her faithful help and precious advices to complete this work.

Abstract

Ischemic stroke is one of the most common causes of death worldwide and it is most often caused by thrombotic process. C-reactive protein and homocysteine have been associated with underlying inflammatory process of atherosclerosis. We investigated the level of high sensitivity CRP and homocysteine during acute period of ischemic stroke in diabetic and non diabetic patients and evaluated relationship between their levels and other risk factors levels. homocysteine and hs CRP were measured in 50 patients with acute stroke and 5 healthy controls. Patients were classified into three groups , Group (I) which included Patients who are not diabetic and have acute ischemic stroke ; they were 25 patients . Group (II) which included Diabetic patients with acute ischemic stroke . It included 25 patients and Group (III) It included 5 normal subjects. Overall 80% of our patients had elevated levels of hs CRP and mean hs CRP level of our patients was elevated and it was significantly higher than in controls (P= 0.001). Only 26% of patients had elevated homocysteine level and mean homocysteine level was normal and not significantly different from controls (P=0.35). No difference was found between diabetic and non diabetic patients in levels of hs CRP and homocysteine. Conclusion: Elevated levels of hs CRP could be considered as a risk factor for acute ischemic stroke but it is difficult to consider homocysteine as so according to our results.

Key words : Homocysteine - Stroke – high sensitivity CRP - Diabetes

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List of abbreviation

ADP	Adenosine diphosphate
AFCAPS/TexCAPS	the Air Force/ Texas Coronary Atherosclerosis Prevention Study
AGEs	Advanced glycosylation end products
Apo B	apolipoprotein B
Apo E	apolipoprotein E
AR	Aldose Reductase
AT	Antithrombin
BEC	Bovine endothelial cells
bFGF	basic fibroblasts growth factor
BMI	Body mass index
BP	Blood Pressure
CAD	Coronary artery disaese
CCA	Common carotid artery
CD	Cluster determinant
CD 40 L	Cluster determinant 40 ligand
CHD	Coronary heart disease
CRP	C reactive protein
EBCT	Electron beam computed tomography
eNOS	Endothelial nitric oxide synthase
ET-1	Endothelin -1
FAD	Food drug adminstration
Hcy	Homocysteine
H2O2	Hydrogen peroxide
HDL	High denisty lipoprotein
HRT	Hormone replacement therapy
Hs CRP	Highly sensitivity C reactive protein
HUVEC	Human umbilical vein endothelial cells
ICAM-1	Intracellular adhesion molecule -1
IL	Interleukin
IMT	Intima media thickness
LDL	Low denisty lipoproatein
Lp-PLA2	lipoprotein associated phospholipase A2
m RNA	Messenger Ribonucleic Acid
MAC	Membrane attack complex
MARCO	Macrophage receptor with collagenous structure
MCP-1	Monocyte chemotactic protein 1
M-CSF	Monocyte colony stimulating factor
MHC	Major histocompatibility complex
MI	Myocardial infarction

MRI	Magnetic resonanance imaging
MTHFR	Methyl tetrahydrofolate reductase
NADPH	Nicotinamide adenine dinucleotide phosphate H
NF- κβ	Nuclear factor κβ
NHANES	the National Health and Nutrition Examination Survey
NIDDM	Non insulin dependent diabetes mellitus
NO	Nitic oxide
PAI-1	Plasminogen activator inhbitor 1
PDGF	Platelet derived growth factor
PKC	Protein kinase C
RAGE	Receptor for Advanced glycation end products
ROS	Reactive oxygen species
RR	Relative risk
SAA	Serum amyloid A
SCI	Silent cerebral infarctin
SDH	Sorbitol dehydrogenase
SNOHO	S-nitosohomocysteine
SR-A	Scavenger receptors class A
SR-B1	Scavenger receptors class B1
t- PA	Tissue plasminogen activator
TF	Tissue factor
tHcy	Total homocysteine
TM	Thrombomodulin
TNF α	Tumor necrosis factor α
TXA2	Thromboxane A2
V-CAM-1	Vascular cell adhesion molecule -1
VLA -4	Very late activation molecule -4
WHO	World Health Organization

Introduction

Acute coronary syndromes, stroke and sudden death are common complications of a disrupted atherosclerotic plaque. Unstable plaque is a result of multiple factors but is commonly characterized by an infiltrate of inflammatory cells. Medical research strongly supports a role for inflammation in pathogenesis , progression and disruption of atherosclerotic plaque.
(Blake , 2003).

About half of patients presenting with myocardial infarction do not have the classic risk factors. This has stimulated a research for other factors that may be responsible and ,when present , may help to predict which patients are at greatest risk for myocardial infarction and other cardiovascular events. With improved understanding of the pathogenesis of ischemic cardiovascular disease, we have gleaned new insights into potential markers of underlying atherosclerosis and cardiovascular risk. In recent years, data suggesting that certain markers of inflammation -- both systemic and local -- play a key role in the development and progression of atherosclerosis , and in its final clinical complications have accumulated.
(Wilson et al , 2006).

C-reactive protein and plasminogen activator inhibitor -1 are circulating markers of low-grade inflammation , thrombosis ,vascular injury. Together with homocysteine , they have been associated with the underlying inflammatory processes and are considered to be "nontraditional" risk factors of atherosclerosis . ***(Theuma and Foneseca , 2003)***.

Hypothesis

High sensitivity CRP and homocysteine might not have a role in the development of cerebrovascular disease.

Aim of the work

Our aim is to investigate the role of nontraditional risk factors of atherosclerosis High sensitivity CRP and homocysteine in the development of stroke in diabetic and non diabetic patients.

CHAPTER 1

DEFINITION AND MECHANISM OF ATHEROSCLEROSIS

DEFINITION AND MECHANISM OF ATHEROSCLEROSIS

Atherosclerosis constitutes the most common medical and surgical problem. This can be manifest clinically as stroke, coronary artery disease, or peripheral vascular disease. Different studies attach various figures to the incidence of these clinical entities. In one study the total incidence rate of stroke per 100,000 person-years was 158***. (Johansson et al, 2000)***.

The Definition of Atherosclerosis :

Atherosclerosis is the most common cause of death and serious morbidity in the western world . The World Health Organization (WHO) has predicted that in the near future it will also become the number one cause of mortality in the entire world . ***(Murray and Lopez , 1997).***

Atherosclerotic lesions mainly contain three components:

(1) Cholesterol in the form of cholesterol esters;

(2) Cells consisting mainly of smooth muscles cells , macrophages and other cell types; and

(3) Connective tissue composed of collagen , elastin and glycosaminoglycans. ***(Woolf N , 1990)***.

Atherosclerosis is a disease of the vessels consisting of both degenerative and regenerative processes that initially affect the intima and at a later stage the media at the bifurcations of the major arteries. The term atherosclerosis reflects the two principal components of the lesion; that is, athero from the Greek word for gruel, corresponding to the necrotic core area at the base of the atherosclerotic plaque and

sclerosis from the Greek word for hardening or induration, corresponding to the fibrotic cap at the luminal edge of the plaque.***(Davies and Woolf ,1993)***.

Atherosclerosis is a disease of elastic arteries (i.e. aorta , carotid and iliac arteries) and large and medium –sized muscular arteries (i.e. coronary and popliteal arteries) , whereas smaller arteries rarely become affected . It is part of a family of arterial disorders characterized by thickening and loss of elasticity of vascular wall . The common term used for these diseases is "arteriosclerosis" , which literally means hardening of the arteries***(Murray and Lopez , 1997)*** .

The Genesis of Atherosclerosis

Microscopic Appearance of the Normal Arterial Wall

The walls of the arteries consist of three layers or tunics (figure 1) :

(1) the intima (the innermost layer),

(2) the media (the middle layer), and

(3) the adventitia (the external layer).

The relative thickness of each layer and the particular type of tissue it contains depends on whether the vessel is an elastic artery, a muscular artery, or an arteriole. The elastic arteries, the aorta for example, receive blood directly from the heart and consist mainly of elastin. The recoiling properties of the latter maintain the pressure within the arterial system during diastole. The muscular arteries distribute blood to the different tissues of the body (i.e. muscles) and consist mainly of smooth muscle cells. The latter are innervated by the autonomic nervous system , which alternates the diameter of the arteries according to the blood requirements of the tissues. Finally the arterioles constitute the smallest arteries lying proximal to the capillary beds . They consist mainly of smooth

muscles cells. The arterioles diameter is also regulated by the autonomic nervous system. This ensures the delivery of the blood under low pressure to the thin walled capillaries for the diffusion to take place***.(Ham , 1979)***

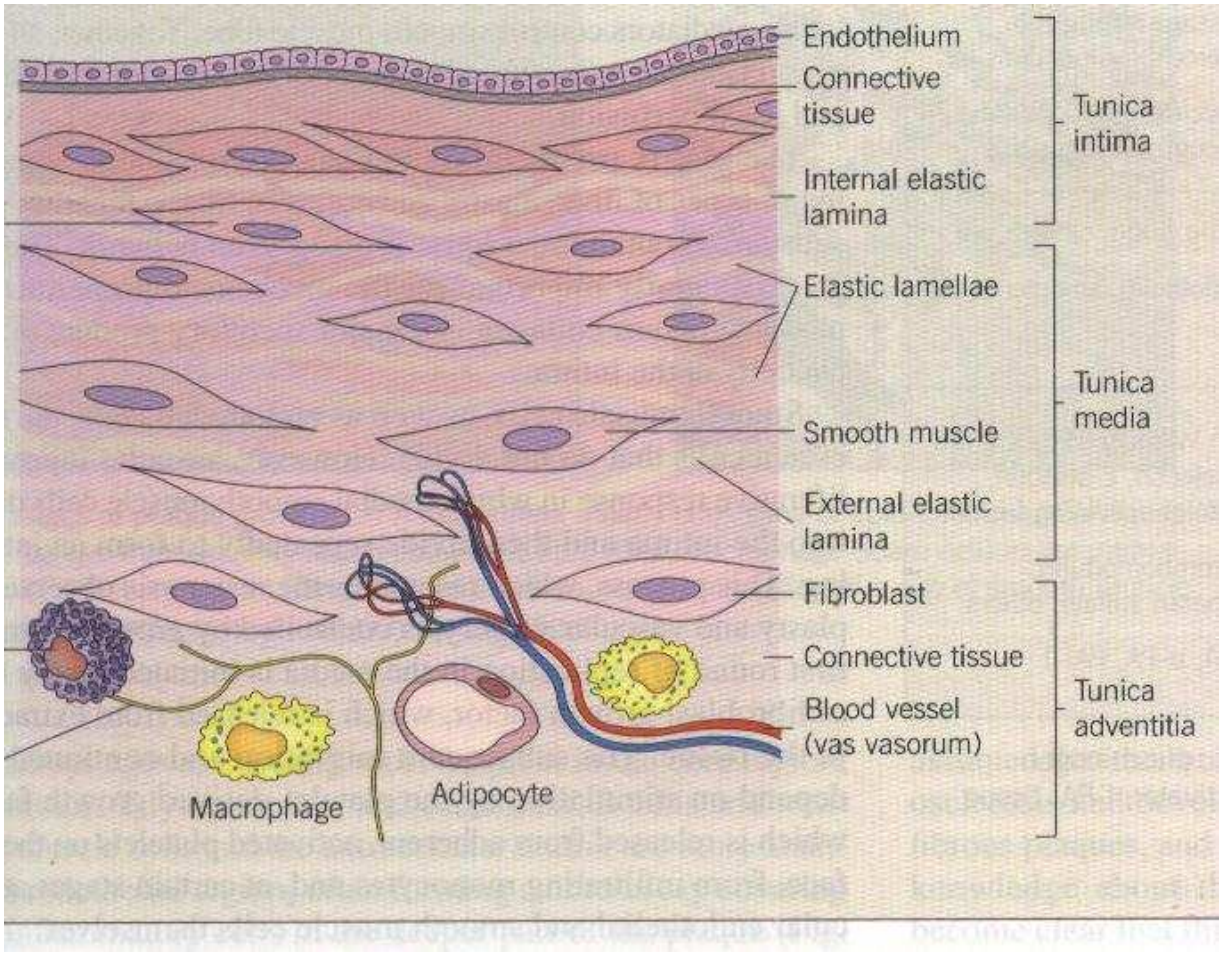

Figure 1
Histologic organization of the normal artery wall
.(Ham, 1979).

The intima is bounded on its inner surface by endothelium and on its outer surface by the internal elastic lamina, which consists of elastin. The space in-between is composed of elastic fibers and incomplete laminae embedded with cells in an amorphous intercellular substance . These cells might be: (1) a relatively undifferentiated type of smooth muscle cells that produce the intercellular substance, (2) fibroblasts, and (3) macrophages. ***.(Ham , 1979).***