The Role Of Inflammation In Stroke: A Recent Update

A Review Submitted For Partial Fulfillment Of
Master Degree ***In Neuropsychiatry***

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List of abbreviations	
AIIA	Angiotensin II antagonist
ABCA١	ATP-binding cassette-transporter family A١
ASS	Acetyl salisalate
ATROCAP	Atorvastatin and Thrombogenicity of the Carotid Atherosclerotic Plaque
AT١	Angiotensin II type ١ receptor
BBB	Blood–brain barrier
CBF	Cerebral blood flow
CSF	Cerebrospinal fluid
CCL	CC chemokine ligand
CD٤٠L	CD٤٠ ligand
CMV	Cytomegalovirus
CRP	C-reactive protein
COX	Cyclo-oxygenase
CVD	Cardio-vascular diseases
ESR	Erythrocyte sedimentation rate
ENA-٧٨	Epithelial neutrophil-activating protein ٧٨
END	Early neurological deterioration
eNOS	Endothelial nitric oxide synthase
ECM	Extracellular matrix
FDA	Food and Drug Administration
GFAP	Glial fibrillary acidic protein
G-CSF	Granulocyte colonystimulating factor
GC	Glucocorticosteroids
HMG-CoA	Hydroxy-٣-methylglutaryl coenzyme A
HMGB١	High-mobility group box ١(cytokine like factor)
HSP	Heat shock proteins

hs CRP	High sensitivity C-reactive protein
١١-HSD١	١١-hydroxysteroid dehydrogenase
INOS	Inducible nitric oxide synthase
IS	Ischemic stroke
IL	Interleukin
I/R	Ischemia/ reperfusion
IL-١β	Interleukin-١ beta
IL-١ra	Interleukin-١ receptor antagonist
ICA	Internal carotid artery
ICAM	Intercellular adhesion molecule
IFN-γ	Interferon-γ
LDL	Low-density lipoproteins
Lp-PLA٢	Lipoprotein-associated phospholipase-A٢
MMP	Matrix metalloproteinases
MIP-١α	Macrophage inflammatory protein ١α
MAdCAM-١	Mucosal addressin cell adhesion molecules
MCP	Monocyte chemoattractant protein
MI	Myocardiac infarction
MHCC-II	Major histocompatibilitycomplex class II
MCAO	Middle cerebral artery occlusion
M-CSF	Macrophage colony stimulating factor
MLN٥١٩	Millenium ٥١٩
NKT	Natural killer T cells
NF-kB	Nuclear transcription factor kappa B
NOS	Nitric oxide synthase
NO	Nitric oxide
OxLDL	Oxidized LDL
PRRs	Pattern-recognition receptors

PAMPs	Pathogen-associated molecular patterns
PDGF	Platelet-derived growth factor
PF-٤	Platelet factor ٤
PET	Positron emission tomography
PECAM-١	Platelet–endothelial cell adhesion molecules-١
PPAR-γ	Peroxisome proliferator-activated receptor-γ
PC	Preconditioning
ROS	Reactive oxygen species
RAGE	Receptor for advanced glycation end producd
RANTES	Regulated on activation, normal T-cell expressed and secreted
SPECT	Single-photon emission computed tomography
SH	Short hairpin
SAA	Serum amyloid A
SUA	Serum uric acid
SVZ	Subventricular zone
TIA	Transient ischemic attack
TGF-β	Transforming growth factor-β
TLRs	Toll-like receptors
TNF	Tumour necrosis factor
tPA	Tissue plasminogen activator
TF	Tissue factor
USPIO	Ultra-small superparamagnetic iron oxide
VCAM-١	Vascular cell adhesion molecule-١
VSMCs	Vascular smooth muscle cells
VLA-٤	Very late activation antigen-٤
WBC	White blood cell count
WHO	World Health Organization

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Introduction and Aim of The Work

Introduction

Stroke: WHO has defined stroke as rapidly developing clinical signs of focal (at times global) disturbance of cerebral function lasting more than ٢٤ hours or leading to death with no apparent causes than that of vascular origin . By conventional clinical definitions, if the neurological symptoms continue for more than ٢٤ hours a person is diagnosed with stroke. Otherwise focal neurological deficits lasting less than one hour is defined as transient ischemic attack (TIA).Such terms defined by the duration of neurological symptoms are redefined with the more wide spread use of sensitive brain imaging such as diffusion-weighted MRI, So patients with symptoms last less than one hour but with an infarction imaged by MRI have been reclassified as having stroke instead of TIA, So the most recent definition of stroke for clinical trials has required either symptoms lasting more than one hour or imaging of an acute clinically relevant brain lesion in a patient with rapidly vanishing symptoms *(Albers et al, ٢٠٠٢)*.

Schemes for assessing a person's risk of a first stroke were evaluated. Risk factors or risk markers for a first stroke were classified according to their potential for modification (no modifiable, modifiable, or potentially modifiable) and strength of evidence (well documented or less well documented). No modifiable risk factors include age, sex, low birth weight, race/ethnicity, and genetic factors. Well-

documented and modifiable risk factors include hypertension, exposure to cigarette smoke, diabetes, atrial fibrillation and certain other cardiac conditions, dyslipidemia, carotid artery stenosis, sickle cell disease, postmenopausal hormone therapy, poor diet, physical inactivity, obesity and body fat distribution. Less well-documented or potentially modifiable risk factors include the metabolic syndrome, alcohol abuse, drug abuse, oral contraceptive use, sleep-disordered breathing, migraine headache, hyperhomocysteinemia, elevated lipoproteins, elevated lipoprotein-associated phospholipase, hypercoagulability, inflammation, and infection *(Goldstein et al, ٢٠٠٦).*

Inflammation

Is defined as the reaction of vascularized living tissues to local injury, it is caused by microbial infections, physical agents, chemicals, necrotic tissue and immunologic reactions. The role of inflammation is to contain and isolate injury, to destroy invading micro-organism and inactivate toxins, and to achieve healing and repair. However inflammation and repair may be potential harmful, causing life-threatening hypersensitivity reactions, progressive organ damage, scarring and fibrosis *(Robbins et al, ٢٠٠٤).*

Inflammation and inflammatory mediators in pathogenesis and complications of stroke

Impact of inflammation on the development of atherosclerotic plaques and their destabilization opens new avenues for treatment, Vaccination against modified low-density lipoproteins (LDL) and heat shock proteins halt plaque progression in experimental atherosclerosis *(Stoll and Bendszus, ٢٠٠٦).*

C-reactive protein (CRP) is involved in the complex pathways leading to endothelial dysfunction, increased peripheral vascular resistance, and large artery stiffness in hypertension. In this regard, the role of C-reactive protein as a marker or a causal factor in promoting hypertension and its complications remains, however, to be elucidated *(Schillaci and Pirro, ٢٠٠٦).*

Inflammatory interactions that occur at the blood-endothelium interface, involving cytokines, adhesion molecules, chemokines and leukocytes, are critical to the pathogenesis of tissue damage in cerebral infarction *(Huang et al, ٢٠٠٦).*

The complement cascade (mainly C٣ activation) has been implicated in ischemia/reperfusion injury, and recent studies have shown that complement inhibition is a promising treatment option for acute stroke *(Mocco et al, ٢٠٠٦).*

Acute ischemic stroke is associated with elevated plasma levels of soluble (s) intercellular adhesion molecules-١ and vascular cellular adhesion molecules-١ (sICAM-١ and sVCAM-١), sEndothelial-selectin (sE-selectin) independent of age, sex and other recognized risk factors for stroke. Decreased levels of sLeukocytic-selectin (sL-selectin) are associated with acute stroke. The observed changes in serum concentrations of adhesion molecules indicate inflammatory process occurring during acute cerebral ischemia *(Simundic et al, ٢٠٠٤)*.

There is a major role for both platelet-associated and endothelial cell-associated Platelets-selectin (P-selectin), as well as neutrophils in the inflammatory and prothrombogenic responses in the microcirculation after focal cerebral ischemia/reperfusion (I/R) *(Ishikawa et al, ٢٠٠٤)*.

Circulating blood cells have been implicated in the pathogenesis of cerebral ischemia/reperfusion (I/R) injury and stroke. I/R promote the adhesion of both platelets and leukocytes in cerebral venules, with the accumulation of adherent leukocytes preceding the recruitment of platelets. Both P-selectin and ICAM-١ contribute to the inflammatory and prothrombogenic state induced by cerebral I/R *(Ishikawa et al, ٢٠٠٣)*.