Is Cerebral Ischemia An Inflammatory Disease? (Relation of acute phase reactant serum ferritin to prognosis of ischemic stroke)

Thesis submitted for partial fulfillment of master degree of *Neuropsychiatry*

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2016

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AMPAr	**:** α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
ApoC	**:** apolipoprotein C
ATP	**:** adenosine triphosphate
Aβ	**:** β-amyloid
BBB	**:** Blood-Brain- Barrier
BDNF	**:** brain-derived neurotrophic factor
BNP	**:** brain natriuretic peptide
Ca+	**:** calcium
CABG	**:** coronary artery bypass graft
CBC	**:** Complete blood count
CBF	**:** cerebral blood flow
CNS	**:** central nervous system
CRP	**:** C- reactive protein
CT	**:** Computed tomography
CVS	**:** Cerebrovascular stroke
DAMPs	**:** damage-associated molecular patterns
DNA	**:** deoxyribonucleic acid
ELFA	**:** Enzyme linked fluorescent assay
END	**:** Early neurological deterioration
ESR	**:** Erythrocyte sedimentation rate
Fe	**:** Iron

GFAP : glial fibrillary acid protein

H2O2 : hydrogen peroxide

H-FABP : heat fatty acid binding protein

HMGB1 : high mobility group box 1

HT : Hemorrhagic transformation

ICAM-1 : The intercellular adhesion molecule 1

ICH : intracerebral hemorrhag

IFN-γ : Interferon gamma

IL-β : Interleukin-**β**

LACI : lacunar infarct

LDL : low-density lipoprotein

Lp-PLA2 : lipoprotein-associated phospholipase A2

MBP : myelin basic protein

MCP-1 : monocyte chemotactic protein-1

MMPs : matrix metalloproteinases

MRI : magnetic resonance imaging

NIHSS : national institute of health stroke scale

NMDA : N-Methyl-D-aspartate

NMDA-R-Ab : N -methyl d -aspartate receptor antibody

NO : nitric oxide

NSE : neuron- specific enolase

OCSP : Oxford Community Stroke Project classification

PACI : partial anterior circulation infarct

PARK7 : Parkinson's disease 7

PFO : patent foramen ovale

PMNs : Polymorphonuclear granulocytes

POCI : posterior circulation infarct

RNA : ribonucleic acid

ROS : reactive oxygen species

SAH : subarachnoid hemorrhage

SODs : superoxide dismutases

SPR : solid phase receptacle

TACI : total anterior circulation infarct

TIA : transient ischemic attack

TLRs : Toll-like receptors

TNFα : tumor necrotizing factor **α**

TOAST : Trial of Org 10172 in Acute Stroke Treatment

t-PA : tissue plasminogen activator

VCAM-1 : vascular cell adhesion protein

WMH : White matter hyperintensities

Introduction

Stroke was the second most frequent cause of death worldwide in 2011, accounting for 6.2 million deaths (~11% of the total). Approximately 17 million people had a stroke in 2010 and 33 million people have previously had a stroke and were still alive. Between 1990 and 2010 the number of strokes decreased by approximately 10% in the developed world and increased by 10% in the developing world. Overall two thirds of strokes occurred in those over 65 years old **(Feigin et al, 2014).**

It is ranked after heart disease and before cancer as a leading cause of death **(Donnan et al, 2008).** In the United States stroke is a leading cause of disability, and recently declined from the third leading to the fourth leading cause of death **(Towfighi and Saver, 2011).**

It is due to the result of either an interruption in blood supply to the brain (ischemic stroke) or bleeding into or around the brain due to a ruptured artery (intracerebral or subarachnoid hemorrhage, ICH or SAH) ***(Lindsay, 2011)***.

Approximately 80% of strokes are ischemic. Preceding a major stroke, many people experience fleeting stroke symptoms, called transient ischemic attack, or a TIA. A person who has had one or more TIAs is almost 10 times

more likely to have a stroke than someone of the same age and sex who has not ***(Lindsay et al, 2011)***.

The newer definition of TIA is "A brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction" ***(Albers et al, 2002).***

Inflammation could promote plaque destabilization within a carotid atherosclerotic lesion, resulting in embolization and subsequent cerebral stroke, and inflammation may progress within freshly infarcted cerebral tissue, further promoting tissue damage ***(Rodriguez-Yanez and Castillo, 2008).***

Reperfusion of cerebral vessels after transient occlusion is associated with immune cell recruitment, which contributes to both damage of the vessel and the surrounding tissue. Polymorphonuclear granulocytes **(PMNs)** are considered to play a prominent role in microvascular responses to ischemia and neuronal cell death during reperfusion ***(Jin et al, 2010).*** This necessitates **PMN** extravasation across the blood–brain barrier (BBB) into the brain parenchyma at early stages after the ischemic insult, prior to terminal neuronal damage ***(Jin et al, 2010).***

Cell adhesion molecules are involved in attraction and recruitment of **PMN** into the site of inflammation and tissue damage, promoting transendothelial migration that involves a series of well-coordinated events between inflamed endothelium and activated **PMN** ***(Jin et al, 2010).*** Firm adhesion of **PMN** to the endothelial cells as well as **PMN** activation is mediated by receptors of the immunoglobulin gene superfamily. Given the involvement of cell adhesion molecules in atherogenesis and response to tissue damage as well as the high circulating levels of their soluble isoforms, soluble cell adhesion molecules have been shown to be associated with disease severity and outcome in stroke ***(Rodriguez-Yanez and Castillo, 2008).***

The pathophysiology of brain injury has guided the development of biomarkers in stroke, including markers of brain tissue damage, markers of immune response and inflammation, markers of endothelial dysfunction, and markers of hemostasis. Evaluated markers have included a variety of proteins, nucleic acids, and lipids which have been studied both as individual markers and in biomarker panels ***(Jin et al, 2010).***

C- reactive protein **(CRP)** is a hepatically derived pentraxin that has important role in the human immune system (***Ridker, 2003).*** This protein is a sensitive nonspecific

marker of systemic low-grade inflammation ***(Pearson et al, 2003)*** and is consistently elevated in the circulation of patients after acute ischemic stroke ***(Emsley et al, 2003).***

As regard CRP, it has been proposed both as a marker of low grade inflammation involved in atherosclerosis and as a predictor of disease progression. The physiologic functions of CRP as an anti-inflammatory scavenger molecule have begun to emerge. Preliminary results of earlier studies reported increased CRP in ischemic stroke patients with notable elevation in comparison to healthy control subjects. ***(montaner et al, 2006).*** This was investigated by ***(Mostafa et al, 2009)*** who found that positive CRP was more associated with cerebral large vessels disease than cerebral small vessels disease but the difference was insignificant.

As regard the outcome of stroke, CRP was found to be associated with poor outcome of stroke. This was investigated by ***(Tork et al, 2009)*** who found that positive **CRP** was associated with low national institute of health stroke scale **NIHSS** score.

The knowledge of new factors associated with a poor response to thrombolysis in stroke patients may help to conceive new strategies to improve the benefit of this treatment. It has recently been shown that high serum ferritin levels are associated with poor functional outcome,

hemorrhagic transformation and severe brain edema in patients treated with i.v. tissue plasminogen activator (t-PA) after ischemic stroke. These findings indicate that increased body iron stores may offset the beneficial effect of thrombolytic therapy ***(Mill´an, 2007).***

The release of free iron from intracellular stores such as ferritin as a result of cerebral ischemia, particularly during reperfusion, catalyses the generation of the toxic free radical hydroxyl which destroys cellular and microvascular integrity ***(Selim and Ratan, 2004).***

Iron intake has been associated with larger infarct volume, greater reactive oxygen species (ROS) generation in brain and peripheral vasculature, glutamate release and inflammatory response after middle cerebral artery occlusion (***Mehta,2004)*** ,whereas iron chelators, antioxidants or ROS scavengers have shown neuroprotective effects reducing infarct size, brain edema and ROS production ***(Romanos et al ,2006).***

Aim of the work

1. To improve the understanding of the acute phase reactant of ischemic stroke patients and to improve our predictors of acute stroke and our predictor of stroke induced infarct size and disability

2. To clarify the role of serum ferritin as one of acute phase reactant in the pathogenesis of cerebral ischemia and to relate its level to the size of brain infarctions and prognostic outcomes of ischemic stroke. This study is a prospective follow up study.

3. To evaluate inflammatory mechanism in cerebral ischemia that might help in management and improvement of cerebral ischemia.

Chapter I

Types and pathogenesis of ischemic stroke

Definition. Ischemic stroke is a condition in which an area of the brain becomes poorly perfused as a consequence of partial or total blockade of an artery. Ischemic stroke is the most common kind of stroke, accounting for near 90% of all strokes. Stroke is the second leading cause of long-term disability in industrialized countries and the second leading cause of death worldwide. **(Rodrigues and Granger, 2014).**

Cerebrovascular stroke **(CVS)** is caused by the interruption of the blood supply, in a particular arterial branch, by thromboembolic or hemodynamics mechanisms, causing metabolic imbalance (high demand versus low supply of oxygen and glucose) in the brain ultimately determining cell death **(Feigin, 2005) .**

At the cellular level, the reduction of cerebral blood flow **(CBF)** and subsequent oxygen depletion trigger biochemical events resulting in phosphorylation and anaerobic metabolism. The anaerobic glycolysis is insufficient and determines the depletion of phosphate reservoir, including adenosine triphosphate **(ATP)** accumulating lactic acid, calcium **(Ca+),** and water. Further,

the cell membrane depolarize and excitatory neurotransmitters are released, particularly glutamate in the axonal endings **(Perlman, 2004).**

Meanwhile, in the cytoplasm, accumulation of free fatty acids will occur, arising from the disintegration of the phospholipidic membrane undergone oxygen peroxidation, free radicals which in turn promotes the formation of more free radicals inside the mitochondria, with the aid of prostaglandins, xanthine and uric acid, and finally in some neurons **Ca+** will induce nitric oxide **(NO)** production **(Perlman and Shalak, 2004).**

The effects from disruption of cellular energy balance, **Ca+** accumulation, lipid peroxidation, acidosis, glutamate release, intense production of free radicals, and **NO** neurotoxicity culminate in cell death Figure(1). **(Junior et al, 2014)**