Role of Interleukin-6 in Ischemic Stroke Outcome

Thesis

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Contents

List of Abbreviations

Abbrev.	Meaning
AF	: Atrial fibrillation
AIS	: Acute ischemic stroke
AMPA	: 1-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
ANP	: Atrial natriuretic peptide
ATP	: Adenosine triphosphate
AUC	: Area under the curve
BBB	: Blood-brain barrier
BI	: Barthel index
BMECs	: Brain microvascular endothelial cells
BNP	: Brain natriuretic peptide
CBF	: Cerebral blood flow
CE	: Cardioembolic
CNS	: Central nervous system
CRP	: C-reactive protein
CSF	: Cerebrospinal fluid
CSS	: Canadian Stroke Scale
CT	: Computed tomography
dl	: Deciliter
DNA	: Deoxyribonucleic acid

ELISA : Enzyme-linked immunosorbent assay

eNOS : Endothelial nitric oxide synthase

FDA : Food and Drug Administration

g : Gram

GCS : Glasgow Coma Scale

gp : Glycoprotein

HbA1c : haemoglobin A1c

HDL : High density lipoprotein

H2O2 : Hydrogen peroxide

hsCRP : High-sensitivity CRP

ICAM : Intercellular adhesion molecules

IFN : Interferon

IL : Interleukin

ISHD : Ischemic heart disease

kg : Kilogram

LAA : Large artery atherosclerosis

LDL : Low density lipoprotein

LIMITS : Levels of Inflammatory Markers in the Treatment of Stroke

M : Microglia

MCA : Middle cerebral artery

MCP : Monocyte chemoattractant protein

mg : Milligram

MI : Myocardial infarction

min : Minute

MIP : Macrophage inhibitory protein

mitoKATP : Mitochondrial ATP-dependent K+

ml : Milliliter

MMPs : Matrix metalloproteinases

MRA : Magnetic resonance angiography

MRI : Magnetic resonance imaging

mRNA : Messenger RNA

mRS : modified Rankin Scale

NIHSS : National Institutes of Health Stroke Scale

NMDA : N-methyl-d-aspartic acid

NO : Nitric oxide

NOMAS : Northern Manhattan Study

O2- : Superoxide anion

OGD : Oxygen glucose deprivation

OH• : Hydroxyl radical

pg : Picogram

PMNs : Polymorphonuclear neutrophils

Ra : Receptor antagonist

RCTs : Randomized clinical trials

RNA : Ribonucleic acid

ROC : Receiver operating characteristics

ROS : Reactive oxygen species

rtPA : Recombinant tissue plasminogen activator

SDF : Stromal cell-derived factor

SPS3 : Secondary Prevention of Small Subcortical Strokes

sRAGE : Soluble receptor for advanced glycation end products

SVO : Small vessel occlusion

TGF : Transforming growth factor

TIA : Transient ischemic attack

TIMP : Tissue inhibitor metalloproteinase

TLR : Toll-like receptor

TNF : Tumor necrosis factor

TOAST : Trial of Org 10172 in Acute Stroke Treatment

Treg : T regulatory

VCAM : Vascular cell adhesion molecule

VLA : Very late antigen

vWF : von Willebrand factor

List of Figures

List of Tables

Stroke is a leading cause of disability in adults that has a heavy social burden worldwide. It is one of the highest causes of mortality, resulting in approximately six million deaths annually ***(Mozaffarian et al., 2016)***.

Inflammatory response plays an important role in the pathophysiology of acute ischemic stroke (AIS) ***(Muir et al., 2007)***. It is involved in the occurrence and development of cerebral ischemia. A higher plasma level of several inflammatory mediators is found in stroke patients compared to the healthy controls ***(Lambertsen et al., 2012)***.

However, the difference of inflammatory response in stroke subtypes remains unclear ***(Brisset et al., 2013)***. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria is the most widely used stroke classification to classify stroke etiology into five subtypes: large artery atherosclerosis (LAA), cardioembolic (CE) stroke, small vessel occlusion (SVO), other determined etiology and undetermined etiology. The classification is mainly based on electrocardiogram, echocardiogram, cervical doppler and magnetic resonance imaging (MRI). ***(Adams et al., 1993)***.

The LAA subtype results in stenosis or occlusion of intra or extracranial large arteries, the instable plaque,

artery to artery embolism and hypoperfusion. The lipohyalinosis, vasoconstriction, arteriosclerosis, and atheroma were suggested as the cause of SVO. The common pathophysiology of LAA and SVO is atherosclerosis and focal inflammation. It is noted that LAA subtype has a higher risk of recurrence and a worse clinical outcome than SVO subtype. It is necessary to determinate the difference of the pathogenesis between LAA and SVO, which is useful for the diagnosis and therapy in non-embolic stroke ***(Jung et al., 2012)***.

On the basis of pathophysiologic differences of each stroke subtype it is possible to hypothesize a different pattern of immuno-inflammatory activation in relation to ischemic stroke subtype. A nonspecific systemic inflammatory response occurs after both ischemic and hemorrhagic stroke, either as a part of the process of brain damage or in response to complications such as deep venous thrombosis. Several studies have reported that higher levels of inflammatory markers such as C-reactive protein (CRP) and interleukin (IL)-6 are associated with worse outcome after ischemic stroke (***Tuttolomondo et al., 2012***).

The most studied cytokines related to stroke are IL-1β, IL-6, IL-10, and tumor necrosis factor (TNF)-α. The proinflammatory cytokines TNF-α, IL-1β, and IL-6 are

secreted in the ischemic region by activated immune cells, which drive the inflammatory process and accelerate additional inflammatory processes by inducing the expression of inflammatory molecules. These molecules recruit more circulating leukocytes, which infiltrate the ischemic region and lead to further loss of neuronal cells and brain tissue, thereby possibly enlarging the cerebral infarct area ***(Kriz and Lalancette-Hébert, 2009)***.

IL-6 is an essential inflammatory mediator and significant elevation of IL-6 levels have been reported in stroke patients shortly after the ischemic event. The source of the early surge in circulating IL-6 levels in stroke has been a matter of controversy for some time. In fact, many cell types including all the major cell types in brain tissue are capable of synthesizing IL-6 ***(Andreassen et al., 2005)***.

Several studies have examined whether the inflammatory response following acute ischemic stroke is related to infarct volume and stroke subtype. The results are inconsistent, thus the roles of the cytokines involved are still unclear (***Lerdal et al., 2011***).

To study whether the level of IL-6 following ischemic stroke is related to severity of stroke, infarct volume, stroke subtype and its impact on stroke outcome.