

Role of Interleukin-6 in Ischemic Stroke Outcome

Thesis

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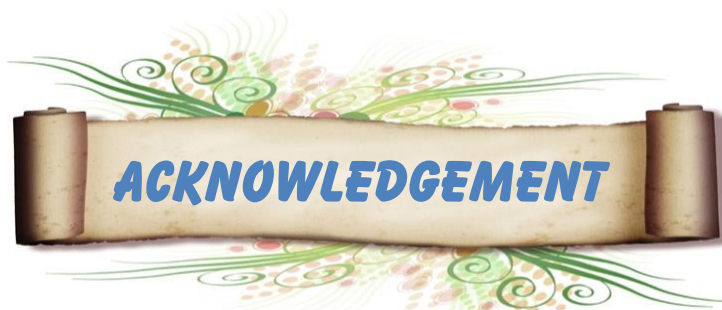
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Contents

Subjects	Page
List of abbreviations.....	II
List of Figures.....	VII
List of Tables.....	IX
• Introduction	1
• Aim of the Work	4
• Review of Literature	
♦ Chapter (1): Stroke and Inflammation	5
♦ Chapter (2): Role of Biomarkers in Acute Cerebrovascular Disease	38
♦ Chapter (3): IL-6 in Cerebrovascular Stroke	52
♦ Chapter (4): Anti-Inflammatory Treatments in Ischemic Stroke	60
• Patients and Methods	84
• Results	89
• Discussion	111
• Conclusion	119
• Recommendations	120
• Summary	121
• References	123
• Appendix	166
• Arabic Summary	

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

List of Abbreviations

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

List of Abbreviations

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

List of Abbreviations

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

No.	Figure	Page
<u>1</u>	Cerebral ischemic cascade.	7
<u>2</u>	Post ischemic inflammation.	16
<u>3</u>	Inflammatory cells in post-ischemic brain injury.	17
<u>4</u>	The inflammatory penumbra concept after ischemic stroke.	28
<u>5</u>	The contribution of inflammation to the development of an atherosclerotic plaque.	30
<u>6</u>	The proposed role of infection and inflammation in AIS.	31
<u>7</u>	Potential biomarkers of stroke categorized according to their role in the ischemic cascade.	39
<u>8</u>	Diagnostic and prognostic markers in ischemic stroke.	48
<u>9</u>	Anti-inflammatory treatments in stroke pathophysiology.	60
<u>10</u>	Graphic representation of the risk factors	90
<u>11</u>	Pie chart showing stroke site	91
<u>12</u>	Pie chart showing different causes of death	92
<u>13</u>	Kaplan Meier curve showing time of death in months	93
<u>14</u>	Pie chart displaying different stroke subtypes among the study population	94
<u>15</u>	Boxplot representation of NIHSS on admission	97
<u>16</u>	Boxplot representation of NIHSS at 3 months	97
<u>17</u>	Boxplot representation of mRS on admission	98
<u>18</u>	Boxplot representation of mRS at 3 months	98

No.	Figure	Page
<u>19</u>	Boxplot representation of mean of IL-6 level in different stroke subgroups	100
<u>20</u>	Graphic representation of the correlation between mRS on admission and IL- 6	102
<u>21</u>	Graphic representation of the correlation between NIHSS on admission and IL-6	102
<u>22</u>	Graphic representation of the correlation between NIHSS after3 months and IL-6	103
<u>23</u>	Graphic representation of the correlation between mRS after 3 months and IL-6	103
<u>24</u>	Graphic representation of the correlation between IL-6 levels and stroke volume	104
<u>25</u>	Means plot between IL-6 levels against recurrence	106
<u>26</u>	Graphic representation of comparison between mean rank of IL-6 in alive patients and cardiovascular related mortalities	107
<u>27</u>	Clustered bar charts showing the levels of IL-6 among cardiovascular related mortality and recurrence	107
<u>28</u>	Clustered bar chart showing the association between recurrence and different stroke subgroups	109
<u>29</u>	Clustered bar chart showing the association between cardiovascular related mortality and different stroke subgroup	109
<u>30</u>	ROC displaying specificity and sensitivity of IL-6 in predicting recurrence	110

List of Tables

<u>No.</u>	<u>Table</u>	<u>Page</u>
<u>1</u>	Biomarkers associated with cause of ischemic stroke	49
<u>2</u>	Demographic data	89
<u>3</u>	Description of compliance, recurrence and mortality among cases	92
<u>4</u>	Distribution of patients among the different Stroke subtypes	93
<u>5</u>	Association between patient's risk factors, gender, stroke site and different stroke subgroups	95
<u>6</u>	Comparison of mean of NIHSS & mRS on admission and at 3 months	96
<u>7</u>	Comparing means of IL-6 values among different stroke subgroups	99
<u>8</u>	Correlation between IL- 6 levels and both NIHSS & mRS levels on admission and after 3 months	101
<u>9</u>	Correlation between IL-6 and stroke volume	104
<u>10</u>	Comparing mean values of IL-6 among recurrence and cause of death	106
<u>11</u>	Association between cardiovascular related mortality, and different stroke subgroups	108

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-1 β , IL-6, IL-10, and tumor necrosis factor (TNF)- α . The proinflammatory cytokines TNF- α , IL-1 β , 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.