POST-STROKE INFECTION: CLINICAL AND IMMUNOLOGICAL STUDY

Thesis

Submitted for Complete Fulfillment of
The Master Degree (M.Sc.) in
Neuropsychiatry

By

MOHAMED ABDEL-GHAFFAR TAHA
(M.B.; B.Ch., Cairo University)

Under supervision of

PROF. DR. MOHAMED ELSAYED ALAWADI
Professor of Neurology,
Faculty of Medicine, Cairo University

DR. HALA ABD EL-MAGEED SHAHEEN
Assistant Professor of Neurology,
Faculty of Medicine, Fayoum University

DR. MERVAT MAMDOOH KHORSHIED
Assistant Professor of Clinical and Chemical Pathology,
Faculty of Medicine, Cairo University

Faculty of Medicine,
Cairo University
2012

تقرير جماعي

عن مناقشة رسالة الماجستير الخاصة بالطبيب/ محمد عبد الغفار طه عبد المجيد
توطئة للحصول على الماجستير في الأمراض العصبية والنفسية

اجتمعت لجنة المناقشة والحكم على الرسالة المقدمة من الطبيب/
محمد عبد الغفار طه عبد المجيد توطئة للحصول على درجة الماجستير في الأمراض العصبية والنفسية المشكلة بقرار من مجلس الكلية والمعتمد من السيد الأستاذ الدكتور/ نائب رئيس الجامعة للدراسات العليا وتتكون من السادة الأساتذة:

أ.د. محمد السيد العوادي	أستاذ الأمراض العصبية كلية طب قصر العيني
أ.د. هالة عبد المجيد شاهين	أستاذ م الأمراض العصبية كلية طب جامعة الفيوم (عن المشرفين بصوت واحد)
أ.د. نيرفانا محمد الفيومي	أستاذ الأمراض العصبية كلية طب قصر العيني (ممتحن داخلي بصوت واحد)
أ.د. محمد عزت علوان	أستاذ ورئيس الأمراض العصبية كلية طب جامعة المنوفية (ممتحن خارجي بصوت واحد)

وذلك بمشيئة الله تعالى يوم الخميس ٢٠١٢/٤/٢٦ بقاعة المؤتمرات بكلية طب قصر العيني – جامعة القاهرة

الرسالة مكونة من ١١٥ صفحة + ملخص باللغة العربية ٢ صفحة
وشملت دراسة إكلينيكية ومناعية في عدوى ما بعد السكتة الدماغية وقياس نسبة خلايا تي الليمفاوية المنظمة وقياس شدة المرض عن طريق المقياس الدولي للسكتة الدماغية.

القـــرار

قررت اللجنة بعد المناقشة:- قبول الرساله

أ.د. محمد السيد العوادي
أ.د. هالة عبد المجيد شاهين

أ.د. نيرفانا محمد الفيومي

أ.د. محمد عزت علوان

بسم الله الرحمن الرحيم

ACKNOWLEDGEMENT

I would like to start their humble work by expressing my deepest gratitude to all the team that helped me in achieving it.

I wish to thank our Professor Dr. ***MOHAMED EL-SAYED ALAWADI****, Professor of Neurology, Faculty of Medicine, Cairo University; who honored me by carrying out the burden of meticulously revising my script and guiding my thoughts.*

I would like to express my sincere thanks and deep gratitude to Dr. ***HALA SHAHEEN,*** *Assistant Professor of Neurology, Faculty of Medicine, Fayoum University, for her energetic follow up with constructive advice, criticism and creative suggestions.*

I am deeply indebted to Dr. ***MERVAT MAMDOOH KHORSHIED,*** *Assistant Professor of Clinical and Chemical Pathology, Faculty of Medicine, Cairo University, whose kindness was more than encouraging.*

I am also profoundly grateful to Dr. ***SAYED SOBHY ELSAYED****, Lecturer of Neurology, Faculty of Medicine, Fayoum University, for his brotherly guidance and enormous support that was a great help to me.*

Last, but not least, I would like to thank all members of the Department of Neurology, Faculty of Medicine, Cairo and Faymoum Universities for their help.


TO THE MEMORY OF MY
FATHER AND MOTHER
TO MY BROTHER
TO MY BELOVED WIFE AND
MY SON OMAR
I DEDICATE THIS WORK

CONTENTS

Page

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Background: Infections are leading cause of death in patients with acute stroke. Recent studies indicate that stroke leads to changes in the immune system which predisposed to infection. **Aim of work:** The objectives of this study are to define the contribution of specific populations of lymphocytes; CD4+CD25 (T-regulatory cells) lymphocytes; to post-stroke infection, their relation to degree of neurological deficit associated with stroke. **Patients and Methods:** Twenty-five patients with acute ischemic stroke subjected to clinical assessment and NIHSS score and flowcytometric analysis for T-regulatory cells. **Results:** T-regulatory cell were statistically significant higher in stroke patient compared to the control group. Seven patients with acute stroke developed infection six had chest infection and one had urinary tract infection. Patients with infection have statistically significant higher NIHSS scale. No significant differences were encountered between stroke patients with and without infection in CD_4, CD_{25} and CD_4 CD_{25} ratio **Conclusion:** Infection prevalent in stroke patient, immune changes was documented in stroke patient but not in patient with and without infection.

Keywords:

Acute ischemic stroke
Infection
Clinical immunology

ABBREVIATIONS

A/G	Adenine/Gunine
ACEIs	Angiotensin-converting enzyme inhibitors
ADP	Adenosine diphosphate
APL	Antipiatelets
APP	Acute phase proteins
Asp.	Aspartate
BBB	Blood brain barrier
C/EBP	Enhancer-binding protein
C1-q	Complement-1
C-3	Complement-3
CARE	Cholesterol and recurrent events
CBC	Complete blood count
CD	Cluster of differentiation
CD40L	CD40 ligand
CE	Cardioembolic
cGMP	Cyclic guanosine monophosphate
CHD	Coronary heart diseases
CHO	Cholesterol
Cp	Ceruloplasmin
CRP	C-reactive protein
CRP-teg	CRP-transgenic
CSF	Cerebrospinal fluid
CT	Computed Tomography
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECs	Endothelial cells
eNOS	Endothelial nitric oxide synthase
E-selectin	Endothelium selectin
ESR	Erythrocyte sedimentation rate
FBS	Fasting blood sugar
G/C	Guanine/Cytosine
G/T	Guanine/Thyamine
GOS	Glasgow Outcome Scale
HDL	High-density lipoprotein cholesterol
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
Hp	Haptoglobin
Hs-CRP	High sensitivity CRP

ICAM	Intercellular adhesion molecule
IFN	Interferon
IgM	Immunoglobulin-M
IHD	Ischemic heart disease
IL	Interleukin
LACI	Lacunar infarction
LDL	Low density lipoprotein
LOX-1	Low density lipoprotein receptor-I
LVD	Large vessel disease
MCA	Middle cerebral artery
MCP-1	Monocyte chemoattractant protein- I
MHCs	Major histocompatability complexes
MI	Myocardial infarction
MMPs	Matrix mellaoproteinases
MMSE	Mini-Mental State Examination test
MRS	Modified Rankin Scale
NCBI	National Center for Biotechnology Information
NF_kB	Nuclear factor-kappa B
NIHSS	National Institute of Health Stroke Scale
NK cells	Natural killer cells
NO	Nitric oxide
OCSP	Oxfordshire Community Stroke Project Classification
oxLDL	Oxidized low-density lipoprotein
PACI	Partial anterior circulation infarction
PAI-1	Plasminogen activator inhibitor-i
PDGF	Platelet-derived growth factor
PMNL	Polymorphonuclear leukocyte
POCI	Posterior circulation infarction
PPAR	Peroxisome proliferators activated receptors
PPBS	Post-Prandial blood sugar
P-selectin	Platelets selectin
RBCs	Red blood cells
RELP	Restriction Fragment Length Polymerase
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SAA	Serum amyloid A
SD	Standard deviation
SMCs	Smooth muscle cells
SNP	Single nucleotide polymorphisms

SPARCL	Stroke Prevention by Aggressive Reduction of Cholesterol Levels
SPSS	Statistical Package for Social Sciences
STATs	Signal transducers and activators of transcription
T/A	Thymine/adenine
TACI	Total anterior circulation infarction
TF	Tissue factor
TGF	Transforming growth factor
TGs	Triglycerides
TIAs	Transient ischemic attacks
TNF	Tumor necrosis factor
TOAST	Trial of Org 10172 in acute stroke treatment
tPA	Tissue-type plasminogen activator
Tyr	Tyrosine
TZDs	Thiazolidinediones
US FDA	United States Food and Drug Administration
UTR	Untranslated regions
UV	Ultra-violet
VCAM	Vascular cell adhesion molecule
VLDL	Very low density lipoprotein
VNTR	Variable numbers of an 86-bp identical tandom repeat
vWF	von Willebrand factor
WBC	White blood cell
WHO	World Health Organization

INTRODUCTION

INTRODUCTION

Acute ischemic stroke is the third leading cause of death and the most frequent cause of permanent disability in adults worldwide. Despite advances in the understanding of the pathophysiology of cerebral ischemia little is known about endogenous counter-regulatory immune mechanism **(Schawrtz et al., 2005)**.

The specific role of T cells in patients with acute stroke and the overall harms and benefits of inflammatory and immune responses remain incompletely understood **(Lakhan et al., 2009)**.

Immune responses follow brain ischemia, may result in systemic immunodepression that predisposes patients after stroke to life-threatening infections **(Meisel et al., 2007)**.

Study of infections complicating the course of acute stroke could address the relevance of immune responses after stroke to stroke associated infection (SAI). SAI may result from a state of stress-mediated reduced immune competence that is associated with increased mortality **(Hori et al., 2003)**.

It is also arguable that reduced immune competence could be beneficial after stroke because it would limit the inflammatory response to brain injury **(Romagnani et al., 2006)**.

Some postulate postischemic alterations in the immune system might represent a useful immunomodulatory adaptation,

preventing autoimmune reactions against CNS antigens after stroke **(Caso et al., 2007)**.

Lymphocyte recruitment and activation are associated with cerebral ischemia-reperfusion injury, the contributions of specific lymphocyte populations to stroke remain unknown **(Liesz et al., 2009)**.

In ischaemic stroke CD4+CD25 (T-regulatory cells) play a key part in controlling immune mechanism **(Garra et al., 2004)**.

A stroke in mice with non-functioning T regulatory cells in their blood caused much greater damage to the brain and greater disabilities than in animals with functioning T regulatory cells. T regulatory cells protect cells by suppressing the harmful activation of the immune system. Depletion of T regulatory cells profoundly increased brain damage with deteriorated functional outcome **(Garra et al., 2004)**.

Recent studies showing that regulatory T cells are major cerebroprotective immunomodulators after stroke suggest that targeting the endogenous adaptive immune response may offer novel promising neuroprotectant therapeutic strategies that target neuro-inflammation and the innate immune system **(Sharma et al., 2007)**.