

Asymptomatic Carotid Atherosclerosis & Silent Brain Infarction in Patients with Metabolic Syndrome

Thesis

Submitted for complete fulfillment of M.Sc. degree in Neurology and Psychiatry

By

Sherif Hassan Elwan

M.B., B. Ch.

Supervised by

Prof. Dr. Tarek Zoheir Tawfik

Professor of Neurology, Cairo University

Prof. Dr. Heba Sayed Assal

Professor of Internal Medicine, National Research Center

Prof. Dr. Foad Abdelmeneem Abdallah

Professor of Neurology, Cairo University

FACULTY OF MEDICINE

CAIRO UNIVERSITY

2014

صدق الله العظيم

التوبة: ١٠٥

تقرير جماعى

لجنة المناقشة والحكم على رسالة الماجستير المقدمة من الطبيب / شريف حسن علوان زكى
توطئه للحصول على درجة الماجستير فى الأمراض العصبية والمشكلة
بقرار من مجلس الكلية والمعتمد من السيد الأستاذ الدكتور / نائب رئيس الجامعة
للدراسات العليا

و تتكون لجنة الحكم من :-

أ.د. طارق زهير توفيق استاذ الأمراض العصبية - جامعة القاهرة (عن المشرفين)

أ.م. نيرمين عادل عبد الغفار أستاذ م.م. الأمراض العصبية (ممتحن داخلى)

أ.د. ليلى نجيب الموصلى أستاذ الأمراض العصبية - - جامعة الأزهر بنات

(ممتحن خارجى)

وذلك بمشيئة الله تعالى يوم السبت الموافق ٢٠١٤/٤/١٢ وذلك بمركز تطوير التعليم
الطبي المتطور بكلية الطب (القصر العينى) جامعة القاهرة

وشملت الدراسة :- تصلب الشريان السباتى والسكتة الدماغية الغير مصاحبين
بأعراض شى مرضى متلازمة الايض .

قررت اللجنة بعد المناقشة: قبول الرسالة

أ.د. طارق زهير توفيق أ.م. نيرمين عادل عبد الغفار أ.د. ليلى نجيب الموصلى

المختص

طارق زهير توفيق
نيرمين عادل عبد الغفار

Acknowledgement

*First and foremost, I'd like to thank almighty **GOD**, for his endless blessings and limitless mercy.*

*It's my pleasure to express my sincere thanks to **Prof. Dr. Tarek Tawfik**, Professor of Neurology, Cairo University, for his generous supervision, continuous encouragement, support and fatherly guidance not just during the thesis, but regarding every aspect in my life. To him I'll always be grateful.*

*I would also like to thank **Prof. Dr. Heba Assal**, Prof. of Internal Medicine, National Research Center, for her kind support, sincere supervision, valuable advice and encouragement throughout this work.*

*I wish to express my sincere thanks and gratitude to **Prof. Dr. Foad Abdallah**, Prof. of Neurology, Cairo University, without whom this work wouldn't have seen the light of day. I'm privileged to be his student and to have participated in this work with him.*

My deepest appreciation and gratitude go to all members of the Neurovascular Ultrasound team in the Neurology department, Cairo University for their selfless help and contribution in the duplex ultrasound work of this study.

*Special thanks to **Dr. Ayman Elbasmy**, Lecturer of Radio-diagnosis, Cairo University for his great effort and cooperation in the brain imaging work of the study.*

*Many thanks to **Dr. Salwa Tawfik**, Researcher of Internal Medicine, National Research Center, for her kind help and support.*

Also I would like to thank all members of the Neurology department in Cairo University for their continuous help, encouragement and support.

Finally, my family; especially my Mom, to whom I owe everything. May I be so successful as to repay you only a little bit of what you have given me throughout life, for that and much more I'm eternally grateful.

Sherif Elwan

Dedication

*To my father: Prof. Dr. Hassan Zaki Elwan, in
hopes that I didn't disappoint you.*



*May you rest in peace and may I be so lucky as
to become the smallest possible version of the
great man that you once were.*

List of contents

	Page
List of abbreviations.....	i
List of figures	ix
List of tables.....	xi
Introduction.....	1
Aim of the work	2
Review of literature :.....	
➤ Metabolic syndrome (diagnosis and risks).....	3
➤ Pathogenesis of Carotid atherosclerosis	15
➤ Atherosclerotic plaque	35
➤ Intracranial Stenosis.....	54
➤ Silent brain infarction	68
Subjects and methods.....	78
Results	89
Discussion	97
Case presentation	110
Summary and recommendations.....	117
References	120
Arabic summary	149

List of abbreviations

AACE	American academy of clinical endocrinologists
ACA	Anterior cerebral artery
ACE	Angiotensin converting enzyme
ADA	American diabetes association
ad-LA	Advanced leukoaraiosis
ADMA	Asymmetric dimethylarginine
AF	Atrial fibrillation
AHA	American heart association
ANS	Autonomic nervous system
Apo-A I	Apolipoprotein A I
Apo-B	Apolipoprotein B
Apo-C III	Apolipoprotein C III
Apo-E	Apolipoprotein E
ARIC study	Atherosclerosis risk in communities study
ATP-III	Adult treatment panel III
ATPase	Adenosine triphosphatase
BA	Basilar artery
Bl. P. / BP	Blood pressure
BMI	Body mass index

Ca	Calcium
CARESS	Clopidogrel and Aspirin for reduction of emboli in symptomatic carotid stenosis
CCA	Common carotid artery
CD	Cluster of differentiation
CDC	Centers for disease control and prevention
CEA	Carotid endarterectomy
CEUS	Contrast enhanced ultrasonography
CHD	Coronary heart disease
CHS	Cardiovascular health study
CLAIR	Clopidogrel plus Aspirin for infarction reduction study
CPR	Curved planar reformat
CO	Cardiac output
COX	Cyclo-oxygenase
CRP	C reactive protein
CSF	Cerebrospinal fluid
CT	Computed tomography
CTA	Computed tomographic angiography
CVD	Cardiovascular disease
DM	Diabetes mellitus
DMT2	Diabetes mellitus type 2

DSA	Digital subtraction angiography
dVRS	Dilated Virchow Robin spaces
DWI	Diffusion weighted image
ECA	External carotid artery
ECAD	Extracranial atherosclerotic disease
EDRF	Endothelial derived relaxing factor
EGF	Epidermal growth factor
EGIR	European group for the study of Insulin resistance
FC	Fibrous cap
FDA	Food and drug administration
FFAs	Free fatty acids
FLAIR	Fluid attenuated inversion recovery
FPG	Fasting plasma glucose
FRS	Framingham risk score
GC	Glucocorticoid
g-GT	Gamma glutamyl transferase
GH	Growth hormone
GI	Glucose intolerance
GM	Grey matter
Hb-1Ac	Glycosilated hemoglobin
HDL-C	High density lipoproteins cholesterol

HHCY	Hyperhomocystinemia
HLA	Human leucocytic antigen
HOMA-IR	Homeostatic model assessment of insulin resistance
HPA axis	Hypothalamo pituitary adrenal axis
hs-CRP	High sensitivity C reactive protein
HSD	Hydroxysteroid dehydrogenase
HTN	Hypertension
ICA	Internal carotid artery
ICAD	Intracranial atherosclerotic disease
ICAM	Intercellular adhesion molecule
ICD	International classification of disease
ICS	Intracranial stenosis
IDF	International diabetes federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IHD	Ischemic heart disease
IL	Interleukin
IMT	Intima media thickness
IR	Insulin resistance
IRS	Insulin receptor substrate
ISSYS	Investigating silent strokes in hypertensives

IVF	In vitro fertilization
LA	Leukoaraiosis
LDL-C	Low density lipoprotein cholesterol
LpA	Lipoprotein A
LP-PLA2	Lipoprotein associated phospholipase A2
MAP	Mitogen activated protein
MCA	Middle cerebral artery
MCP	Monocyte chemotactic protein
MetS	Metabolic syndrome
MI	Myocardial infarction
mi-RNA	Micro RNA
MMPs	Matrix metalloproteinases
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MRIPH	MRI defined plaque hemorrhage
mRNA	Messenger RNA
MRP	Myeloid related protein
NADP	Nicotinamide adenine dinucleotide phosphate
NCEP	National cholesterol education program
NF-Kb	Nuclear factor Kb
NHLBI	National heart, lung and blood institute

NIH	National institutes of health
NIHSS	National institutes of health stroke scale
NIVE	Non invasive vascular elastography
NKT	Natural killer T cells
NO	Nitric oxide
NOS	Nitric oxide synthase
OSS	Oscillatory shear stress
PAI-1	Plasminogen activator inhibitor 1
PCA	Posterior cerebral artery
PD	Proton density
PDGF	Platelet derived growth factor
PET	Positron emission tomography
PI	Phosphatidylinositol
Pl. GF	Placental growth factor
PSGL	P selectin glycoprotein ligand
PTAS	Percutaneous transluminal angioplasty and stenting
P value	Probability value
PWMLs	Periventricular white matter lesions
ROS	Reactive oxygen species
SAMMPRIS	Stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis trial

SBI	Silent brain infarction
SD	Standard deviation
SII	Surface irregularity index
SIVD	Subcortical ischemic vascular disease
SLI	Symptomatic lacunar infarct
SMC	Smooth muscle cell
SNS	Sympathetic nervous system
SONIA	Stroke outcomes and neuroimaging of intracranial atherosclerosis trial
SPSS	Statistical package for the social science
STA	Superficial temporal artery
SVD	Small vessel disease
TCCD	Transcranial colour coded duplex ultrasonography
TCD	Transcranial Doppler
TGF- β	Transforming growth factor beta
TGs	Triglycerides
Ths	T helper cells
TIA	Transient ischemic attack
TLR	Toll like receptor
TNF α	Tumor necrosis factor alpha
TOF	Time of flight

TOSS 2	Trial of Cilostazol in symptomatic intracranial stenosis 2
t-PA	Tissue plasminogen activator
T reg	T regulatory cells
U/S	Ultrasonography
USA	United states
USPIO	Ultrasmall superparamagnetic iron oxide
VA	Vertebral artery
VB	Vertebro-basilar
VC	Vasoconstriction
VCAM	Vascular cell adhesion molecule
VLDL	Very low density lipoprotein
VRS	Virchow Robin spaces
vWF	Von Willebrand factor
WASID	Warfarin aspirin symptomatic intracranial disease trial
WC	Waist circumference
WI	Weighted image
WM	White matter
WMLs	White matter lesions
WHO	World health organization
WSS	Wall shear stress

List of figures

Number	Title	Page
(1)	Anatomy of the arterial wall	16
(2)	Summary of normal endothelial functions and consequences of endothelial dysfunction	31
(3)	B mode and duplex ultrasound images of the common carotid artery showing an ulcerated atherosclerotic plaque at the origin of the internal carotid artery	44
(4)	B mode ultrasound showing 2 plaques of markedly different surface irregularity indices	45
(5)	B mode ultrasound showing a hypoechoic homogenous plaque and a hyperechoic heterogenous plaque	47
(6)	Multidetector CT angiography showing different plaques and stenosis	48
(7)	Axial MRI images of specific AHA lesion type VI plaque features in a patient with acute ischemic infarct	50
(8)	Contrast-enhanced ultrasound image of the common carotid artery with an ulcerated atherosclerotic plaque in the carotid bulb	52
(9)	Phillips HDI 5000 U/S equipment	80