ROLE OF ANGIOTENSIN CONVERTING ENZYME AND ITS GENETIC POLYMORPHISM IN ISCHEMIC STROKE PATIENTS

Thesis

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ABSTARCT

OBJECTIVE: To investigate the role of Angiotensin Converting Enzyme and its (insertion/deletion) polymorphism in Egyptian ischemic stroke patients. **METHODS:** Case control study including 20 non-hypertensive ischemic stroke patients, 20 hypertensive ischemic stroke patients and 20 age and sex matched hypertensive control subjects. Genotyping was performed using polymerase chain reaction (PCR) method. Serum ACE levels were measured by ELISA method. **RESULTS:** The frequency of DD genotypes were significantly higher in stroke cases (42.5%) compared to control subjects (10%) (p=0.02). ACE serum levels in non-hypertensive stroke patients, hypertensive stroke patients, and control subjects were 51.2±6.9, 40.3±6.9 and 33.3±3.7 (IU/L) respectively, (p<0.001). Patients on ACEIs prior to their stroke had a less severe stroke on presentation and better stroke outcome after 3 months as compared by the NIHS and SSS. **CONCLUSION:** ACE "DD" genotype is a risk factor for ischemic stroke. ACE serum levels are higher in stroke patients compared to control group, and higher ACE serum levels correlates with both stroke severity and worse stroke outcome.

KEYWORDS:

Egypt, stroke, ACE gene polymorphism, ACE serum level, HTN

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ABBREVIATIONS

3Ms	Modified mini-mental examination
ACE	Angiotensin Converting Enzyme
ACE2	Angiotensin Converting Enzyme 2
ACEIs	Angiotensin converting enzyme inhibitors
AD	Alzheimer's disease
AF	Atrial fibrillation
Ang I	Angiotensin I
Ang II	Angiotensin II
ARB	Angiotensin receptor blocker
AT1R	Angiotensin II type 1 receptor
AT2R	Angiotensin II type 2 receptor.
BH4	tetrahydrobiopterin
BP	Blood pressure
CBF	Cerebral blood flow
CCB	Calcium-channel blocker
CI	Confidence interval
DNA	Deoxyribonucleic acid
DRIs	Direct Renin Inhibitors
ECM	Extracellular matrix
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
GPCR	G-protein coupled receptor
HTN	Hypertension
ICAM-1	Intercellular adhesion molecule-1
IGF-1R	Insulin-like growth factor-1 receptor
IL-6	Interleukin-6
JG	Jusxtaglomerular
JGA	Juxtaglomerular apparatus
JNC7	Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
MAP	Mitogen-activated protein

MAPK	Mitogen-activate protein kinase
MCP-1	Monocyte chemoattractant protein-1
MMPs	Matrix metalloproteinases
NADP	Nicotinamide adenine dinucleotide phosphate
NADPH	Nicotinamide adenine dinucleotide phosphate oxidase
NEP	Neprilysin
NF-kB	Nuclear factor–kB
NIHSS	National Institutes of Health Stroke Scale
NO	Nitric Oxide
NOS	Nitric oxide synthase
PAI-1	Plasminogen activator inhibitor-1
PD	Parkinson's disease
PDGF	Platelet-derived growth factor
PKB	Protein kinase B
PPARs	Peroxisome proliferator-activated receptors
PRA	Plasma Renin Activity
PTP	Phosphotyrosine phosphatase
RAAS	The Renin Angiotensin Aldosterone System
RAS	Renin angiotensin system
ROS	Reactive oxygen species
RXR	Retinoid X receptor
SHR	Spontaneously hypertensive rats
SNP	Single nucleotide polymorphism
SSS	Scandinavian Stroke Scale
TNF-α	Tumor necrosis factor–α
TPA	Tissue plasminogen activator.
VCAM-1	Vascular adhesion molecule-1
VSMC	Vascular smooth muscle cells

Introduction

INTRODUCTION

Angiotensin Converting Enzyme (ACE) plays an essential role in two physiological systems, one leading to the production of angiotensin II and the other to the degradation of bradykinin. The wide distribution and multifunctional properties of these two peptides suggest that ACE could be involved in various pathophysiological conditions including cerebro-vascular ischemia **(Karagiannis et al., 2004).**

The discovery that ACE levels are under genetic control ushered in a new era of investigation; most studies focused on an insertion/deletion (I/D) polymorphism in intron 16 of the *ACE* gene as a marker for a functional polymorphism. Many single nucleotide polymorphisms were detected in the gene and the search for the locations of functional polymorphisms became a topic of extensive investigation **(Günes et al., 2004).**

Several studies described an association between ACE enzyme gene polymorphism and ischemic stroke. **Brenner et al. (2005)** suggested that renin-angiotensin-aldosterone system activity and genes contribute to cerebrovascular disease and post-stroke vascular death in white patients ,these results confirmed the work of **Hong et al. (2007)** who reported that ACE gene polymorphism may be a genetic determinant of ischemic stroke in Korean patients.

In contrast, **Miris et al. (2006)** suggested that ACE gene polymorphism in not associated with pathogenesis of ischemic stroke in Turkish patients. Similar observations were made by **Pera et al. (2006)** who failed to find an association between ACE polymorphism and etiological subtypes of ischemic stroke in a Polish population.