Role of inflammation in intractable temporal lobe epilepsy

A Thesis submitted for partial fulfillment of
MD, Degree in Neurology
By

Salem Taha El sayed
M.B.B.Ch., M. Sc. Ain Shams University

Supervised by

Prof. Mohamad Ossama Abdulghani

Professor of Neurology
Faculty of Medicine Ain-Shams University

Prof. Taha Kamel Taha

Professor of Neurology
Faculty of Medicine Ain-Shams University

Prof. Ayman Mohamed Nassef

Professor of Neurology
Faculty of Medicine Ain-Shams University

Dr. Haytham Mohamed Hamdy

Lecturer of Neurology
Faculty of Medicine Ain-Shams University

Faculty of Medicine
Ain-Shams University
CAIRO, 2014

بسم الله الرحمن الرحيم

" قالوا سبحانك لا علم لنا
إلا ما علمتنا إنك أنت العليم الحكيم

صدق الله العظيم
سورة البقرة

ACKNOWLEDGEMENT

First and foremost, I feel always indebted to ***Allah*** *the most kind and most merciful, as we owe to him for his great care and guidance in every step in our life, and who enabled me to accomplish this work.*

I wish to express my greatest gratitude and ultimate thanks to ***Prof. Mohamad Ossama Abdulghani*** *Professor of Neurology, Faculty of Medicine, Ain Shams University for accepting to supervise this work and for his valuable supervision and guiding comments. He generously devoted much of his precious time and provided unlimited in depth guidance, I sincerely appreciate all the encouragement and support given by him.*

I am profoundly grateful to ***Prof. Taha Kamel****, Professor of Neurology, Faculty of medicine, Ain Shams University, for his close and kind supervision, his constant fatherly advice and support and scientific guidance, for his trust in my performance and my work.*

Acknowledgement

*I am deeply grateful to **Prof. Ayman Nassef**, Professor of Neurology, Faculty of Medicine, Ain Shams University, I am grateful for his helpful notes and valuable recommendations throughout this work. His constant guidance helped me to achieve this work.*

*To **Dr. Haytham Hamdy**, Lecturer of Neurology, Faculty of Medicine, Ain Shams University, I express my sincere appreciation for his patient guidance, constructive remarks and continuous support. He gave genuine and kind help to achieve the best of this work.*

*I would like to express my appreciation to **Madam Mona Adly** and **Mr. Emad Hossam,** the technicians in El Demerdash Pathology department for helping me storing samples and conducting the test. Also, my appreciation to **Mrs. Rasha Mohamed** the epilepsy clinic nurse for helping me in collecting the blood samples from selected patients.*

I would like to extend my thanks to all my professors, colleagues and friends, so many of them influenced, encouraged and inspired me throughout the years.

Last but not least, I wish to express my love and respect to my parents, my wife, my lovely sons and my brother, for your endless love and care, for your valuable emotional support and continuous encouragement which brought the best out of me. I owe you all every achievement throughout my life.

Finally, my thanks should go to all the patients who were the subjects of this work and who cooperated in this research.

List of Tables

List of Figures

TABLE OF CONTENTS

List of Abbreviations

5-HT	5-hydroxyl triptamine
ACH	Acetylcholine
ACTH	Adrenocorticotropic hormone
AED	Antiepileptic drug
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AP	Action potentials
APCs	Antigen presenting cells
AQP 4	Aquaporin 4
BBB	Blood–brain barrier
BDNF	Brain-derived neurotrophic factor
Ca^{2+}	Calcium
cAMP	Cyclic adenosine monophosphate
CBZ	Carbamazepine
Cl^{-}	Chloride
COX-2	Cyclooxygenase-2
CSF	Cerebrospinal fluid
DE	Dentate gyrus
EAAT	Excitatory amino acid transporter
EEG	Electroencephalogram
ENT1/2	Equilibrative nucleoside transporters 1 and 2
EPSP	Excitatory postsynaptic potential
FGF	Fibroblast growth factor
FS	Febrile seizure
FSE	Febrile status epilepticus
GABA	Gamma-aminobutyric acid
GCD	Granule cell dispersion
GFAP	Glial fibrillary acidic protein
HMGB1	High mobility group box 1
HPA	Hypothalamic—pituitary—adrenal
I-Cam	Intercellular Adhesion Molecule

ICE	Interleukin Converting Enzyme
IFNs	Interferons
IGF	Insulin growth factor
IL	Interleukin
ILAE	International League Against Epilepsy
IPSP	Inhibitory postsynaptic potential
IS	Infantile spasms
K^+	Potassium
KCNQ	Potassium Channel, Voltage-Gated, KQT-like subfamily
Kir4.1	Rectifying K^+ channels
LEC	Lateral entorhinal cortex
MCD	Malformation of cortical development
MCP-1	Monocyte chemoattractant protein-1
M-CSF	Macrophage colony stimulating factor
MDR1	Multiple drug resistance 1
MEC	Medial entorhinal cortex
MFS	Mossy fiber sprouting
MMP	Matrix metalloproteinases
MTS	Mesial Temporal sclerosis
MRP	Multidrug resistance protein
Na^+	Sodium
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NMDA	N-methyl-D-aspartate
NO	Nitric oxide
OPC	Outpatient clinic
PAF	Platelet activating factor
PDS	Paroxysmal depolarising shift
PGE2	Prostaglandin E2
P-gp	P-glycoprotein
PTZ	Pentylentetrazole

RMP	Resting membrane potential
SAH	Selective amygdalohippocampectomy
sATR	Standardized anterior temporal resection
SE	Status epilepticus
SSC	Semiological seizure classification
TBI	Traumatic brain injury
TGF-β	Transforming growth factor- β
TLE	Temporal lobe epilepsy
TLR	Toll-like receptor
TNF	Tumor necrosis factor
VNS	Vagal nerve stimulation
V-Cam	Vascular cell adhesion protein
VEGF	Vascular endothelial growth factor
VPA	Valproic acid

Introduction

Epilepsy is a clinically heterogeneous group of disorders; defined as spontaneous occurrence of seizures associated with electric discharges of the brain. Its prevalence is 5-10/1000, 25-30% of patients have intractable epilepsy, epileptic seizures result from excessive discharge in a population of hyper excitable neurons. Most epileptic seizures are due to discharges generated in cortical and hippocampal structures, although subcortical structures are also involved in some seizures types **(Brodie and Kwan, 2002).**

Variety of factors influence the incidence and prevalence of seizures. Reports suggest higher incidence of seizures among patients with chronic inflammatory problems compared to normal population **(Rao et al, 2009).**

Recent findings suggest involvement of inflammation in the pathogenesis and the course of epilepsy through cytokines and other pro inflammatory mediators which includes interleukins, interferons, tumor necrosis factors, chemokines and growth factors, the significance of cytokine production in relation to epileptic seizures is not yet fully known as Interleukin (IL)-1β and Interleukin (IL)-6 have been shown to exert neuroprotective and neurotrophic effects **(Vezzani and Granata, 2005).**

Some cytokines act to make disease worse (proinflammatory), whereas others serve to reduce inflammation and promote healing (anti-inflammatory). Proinflammatory cytokines are harmful to the host, particularly during overwhelming infection. IL-1 and tumor necrosis factor (TNF) are proinflammatory cytokines, and when they are administered to humans, they produce fever, inflammation, tissue destruction, and, in some cases, shock and death. Blocking IL-1 or TNF has been highly successful in some

diseases such as rheumatoid arthritis, inflammatory bowel disease, or graft-vs-host disease **(Dinarello, 2000).**

Major anti-inflammatory cytokines include IL-1 receptor antagonist, IL-4, IL-6, IL-10, IL-11, and IL-13. The functional definition of an anti-inflammatory cytokine is the ability of the cytokine to inhibit the synthesis of IL-1 and TNF. IL-6 has both proinflammatory and anti-inflammatory properties. Although IL-6 act predominantly as an anti-inflammatory cytokine **(Steven and DePalo**, **2000).**

Experimental evidence in rodent models has demonstrated that seizures induce high levels of inflammatory mediators in brain regions involved in the generation and propagation of epileptic activity. This response consists of an increase in prototypic inflammatory cytokines such as interleukin1β, IL-6 and TNF-α in microglia and astrocytes, which is accompanied, and often followed, by a cascade of down-stream inflammatory events (i.e. activation of Nuclear factor-kB, complement system, chemokines, acute phase proteins) **(Vezzani and Granata, 2005).**