شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

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NMDA, AMPA and GABA Receptor Antibodies; Relation to Clinical and Electrophysiological Findings in Drug-Resistant Epilepsy

Thesis

Submitted for Partial Fulfillment of Master Degree
*In **Clinical Pathology***

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2021

سورة البقرة الآية: ٣٢

Acknowledgment

First and foremost, I feel always indebted to **ALLAH**, *the Most Kind and Most Merciful.*

I would like to express my deepest thanks, gratitude and profound respect to my honored professor, ***Prof. Dr., Hala Ahmed Talkhan,*** *Professor of Clinical Pathology, Faculty of Medicine, Ain-Shams University, for her meticulous supervision. I consider myself fortunate to work under her supervision. Her constant encouragement and constructive guidance were of paramount importance for the initiation, progress and completion of this work.*

I would like to extend my thanks to ***Prof. Dr. Mahmoud Hemeda El Rakawi,*** *Professor of Neurology, Faculty of Medicine, Ain-Shams University, for his active participation in this work. He really did her best to get this work fulfilled.*

Also I would like to thank ***Prof. Dr. Dina El Sayed El Shenawy****, Professor of Clinical Pathology, Faculty of Medicine, Ain-Shams University, for her assistance, fruitful participation, and precious advices and guide.*

My special thanks to ***Dr. Doaa Mohamed Abd El-Aziz****, Assistant Professor of Clinical Pathology, Faculty of Medicine, Ain-Shams University, who offered me a lot of guidance, continuous encouragement and advice while supervision every step in this work.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Last but not least my sincere thanks and appreciation to all patients participated in this study.

Ahmed Magdy Tuhami

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List of Abbreviations

Abb.	Full term
AMPA	*α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid*
AED	*Anti-epileptic drugs*
CAMKII	*Ca2+/Calmodulin-dependent Protein Kinase II*
CNS	*Central Nervous system*
DRE	*Drug resistant epilepsy*
E	*Excitation*
EEG	*electroencephalogram*
GABA	*Gamma aminobutyric acid*
I	*Inhibition*
IgG	*Immunoglobulin G*
ILAE	*International League Against Epilepsy*
IPSP	*Inhibitory postsynaptic potential*
MAC	*Membrane attack complex*
NMDA	*N-methyl-D-aspartate*
R	*Receptor*
RE	*Rasmussen's encephalitis*
TLR	*Toll - like receptors*

INTRODUCTION

Epilepsy is a neurological disorder characterized by sudden recurrent episodes of convulsions, sensory disturbance, or loss of consciousness, resulting from abnormal electrical brain activity. According to The International League against Epilepsy, the condition is defined by at least 2 unprovoked seizures more than 24 hours apart. Affecting more than 70 million people worldwide, this disorder takes on a various forms, patterns, and severity ***(Singh and Trevick, 2016).***

In epilepsy, the firing threshold of excitatory neurons is decreased. This may occur due to changes in the ion channels or improper functioning of inhibitory neurons. This in turn results in the formation of a seizure focus, which is a specific area from which seizures may develop. Another mechanism, may be due to the up-regulation of excitatory circuits or down-regulation of inhibitory circuits following brain injury ***(Goldberg and Coulter, 2013).*** These secondary epilepsies occur through a process called epileptogenesis. Failure of the blood–brain barrier may also be a mechanism ***(Obey and Janigro, 2006).***

Anticonvulsant medications are the cornerstone of epilepsy treatment, which may continue for lifetime of the patient. Treatment modality is based on seizure type, epilepsy syndrome, other medications used, other health problems, and

the person's age and lifestyle. Initially, a single medication is recommended; if control is not achieved, changing to a single other medication is recommended. If the second medication fails, two medications at once are recommended then ***(National Clinical Guideline Centre, 2012).***

Failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drugs to achieve sustained seizure freedom is known as drug-resistant epilepsy ***(Kwan et al., 2000)***. It is commonly diagnosed several years after uncontrolled seizures, although in most cases it is evident much earlier. Around 30% of epilepsy patients have a drug-resistant form ***(Brodie, 2013).***

In recent years, three types of synaptic receptors have been the subject of research in regarding their role in the normal physiology of the nervous system, and their involvement in various neurological conditions. These receptors include the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, *N*-methyl-D-aspartate (NMDA receptor) receptor and Gamma-aminobutyric acid (GABA) receptor ***(Kayser and Dalmau, 2016).***

Auto-antibodies against synaptic receptors have been detected in a number of neurological conditions such as anti-NMDA receptor encephalitis and limbic encephalitis. It is possible that such antibodies maybe the underlying cause of drug resistant epilepsy.

Aim of the Work

We aim to determine whether autoantibodies against AMPA, NMDA and GABA receptors are present in drug-resistant epilepsy and their correlation with clinical and electrophysiological findings.

1. EPILEPSY

1.1. Overview

Epilepsy is a group of neurological disorders characterized by recurrent eipsodes of epileptic seizures ***(Fisher et al., 2014).*** These episodes vary in duration; from brief and almost undetectable periods to long periods of severe muscle contractions. These episodes can lead to physical injuries, such as fractures, tongue biting and head trauma ***(Chang, 2003).***

The International League against Epilepsy (ILAE) as of 2014 defines epilepsy by any of the following criteria:

- At least **two** unprovoked (or reflex) seizures occurring more than 24 hours apart
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least **60%**) after two unprovoked seizures, occurring over the next 10 years
- Diagnosis of an epilepsy syndrome

1.2. Epidemiology of epilepsy

Epilepsy is one of the most common neurological disorders, affecting around 39 million people as of 2015 ***(Vos et al., 2016).*** It affects 1% of the population by age 20 and 3% of the population by age 75 ***(Holmes, 2008)***, with a slight

predominance in males. 80% of these cases occur in the developing world ***(Newton, 2012).***

1.3. Pathophysiology of epilepsy

The exact mechanism of epilepsy still remains unknown, although some facts are known about its cellular and network mechanisms. However, it is unknown which circumstances lead to a shift in the brain towards the activity of a seizure, and its excessive synchronization ***(Le Van Quyen et al., 2003).***

Under normal conditions, brain electrical activity is non-synchronous; neurons do not normally fire in sync with each other, but rather fire in order as signals travel throughout the brain. This activity is regulated by numerous factors both within the neuron and the cellular environment **(Fig.1).** Such factors within the neuron include the type, number and distribution of ion channels, changes to receptors and changes in gene expression ***(Hammer and McPhee, 2010)***, while factors around the neuron include ion concentration, synaptic plasticity and regulation of transmitter breakdown by glial cells ***(Bulmenfield, 2005).***

In epilepsy, the firing threshold of excitatory neurons during this period is decreased. This may happen due to changes in ion channels or abnormal function of inhibitory neurons. This in turn results in a specific area from which seizures may develop, known as a seizure focus. Another