

# **Serum Homocysteine Level in Chronic Epileptic Patients**

**Thesis**

By

**Ahmad Kamal Shamseldin**

M.B.,B.ch.

Cairo University

Submitted in partial fulfillment of  
Master Degree in Neuropsychiatry

*Supervised by*

**Prof. Dr. Manal Mahmoud Elkattan**

Professor of Neurology

Faculty of Medicine

Cairo University

**Prof. Dr. Amany Mahmoud Rabah**

Professor of Neurology

Faculty of Medicine

Cairo University

**Prof. Dr. Sahar Abdulaaty Sharaf**

Professor of Clinical Pathology

Faculty of Medicine

Cairo University

**Faculty of Medicine**

**Cairo University**

**2010**

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

﴿وَمَا يَسْتَوِي الْأَعْمَىٰ وَالْبَصِيرُ ❀ وَلَا الظُّلُمَاتُ وَلَا النُّورُ﴾

(فاطر: ١٩، ٢٠)

﴿اللَّهُ وَلِيُّ الَّذِينَ آمَنُوا أَخْرِجُوهُمْ مِنَ الظُّلُمَاتِ إِلَى النُّورِ﴾

(البقرة: ٢٥٧)

﴿وَقُلْ رَبِّ زِدْنِي عِلْمًا﴾

(طه: ١١٤)

## Acknowledgement

All thanks to Allah, the Greatest, the most Merciful, in the fashion that He likes and pleases. He gives all His creation guidance and blessings, and I, His humble servant, have received from Him such grace that I could not imagine or describe.

I am deeply indebted to **Prof. Dr. Manal Mahmoud Elkattan**, Professor of Neurology, Faculty of Medicine, Cairo University, for her kind guidance and unlimited support.

My gratitude and appreciation to **Prof. Dr. Amany Mahmoud Rabah**, Assistant Professor of Neurology, Faculty of Medicine, Cairo University. She has spent her time and effort in close supervision of this thesis to be presented in its final shape.

I am thankful to **Prof. Dr. Sahar Abdulaaty**, Assistant Professor of Clinical Pathology, Faculty of Medicine, Cairo University. Her help, support and cooperation made this work possible.

Also, I should thank all my Professors and colleagues for their invaluable advice and help.

Finally, I express my gratitude to my family and friends for their continuous encouragement.

# Contents

	<b>Page</b>
<b>List of figures</b>	<b>v</b>
<b>List of tables</b>	<b>vii</b>
<b>Abbreviations</b>	<b>x</b>
<b>Introduction</b>	<b>xii</b>
<b>Homocysteine chemistry and metabolism</b>	<b>1</b>
<b>Hyperhomocysteinemia</b>	<b>9</b>
<b>The role of hyperhomocysteinemia in disease</b>	<b>21</b>
<b>The relationship between homocysteine and epilepsy</b>	<b>36</b>
<b>Epilepsy: a general overview</b>	<b>49</b>
<b>Subjects and methods</b>	<b>61</b>
<b>Results</b>	<b>72</b>
<b>Case presentation</b>	<b>91</b>
<b>Discussion</b>	<b>100</b>
<b>Summary and conclusions</b>	<b>110</b>
<b>References</b>	<b>115</b>
<b>Appendix</b>	<b>139</b>
<b>Arabic summary</b>	<b>145</b>

## List of figures

<b>Number</b>	<b>Title</b>	<b>Page</b>
Figure 1	Structure of homocysteine.	2
Figure 2	Metabolic pathways for homocysteine formation and removal.	4
Figure 3	Homocysteine metabolism.	6
Figure 4	Folate serum concentrations in patients with epilepsy stratified according to their homocysteine plasma concentration and vitamin B6 plasma concentrations in the same strata of patients.	43
Figure 5	Distribution of seizure types in the total patient group and subgroups.	75
Figure 6	Number and percentage of patients on AEDs monotherapy and polytherapy.	77
Figure 7	Distribution of AED types by percentage in the patient subgroups on treatment.	77
Figure 8	Mean homocysteine level in the patient subgroups.	79
Figure 9	Mean homocysteine level in patients with different seizure types.	82
Figure 10	Mean homocysteine level in patients on monotherapy and polytherapy.	83
Figure 11	Mean homocysteine level in patients on different types of AEDs and combinations.	85
Figure 12	Mean homocysteine level in patients with	87

## List of figures

	sub-therapeutic, therapeutic and toxic serum levels of AEDs.	
Figure 13	A page from the EEG of the patient presented in case 1, showing no abnormality.	92
Figure 14	A page from the EEG of the patient presented in case 2, showing no abnormality.	94
Figure 15	A page from the EEG of the patient presented in case 3, showing left centroparietal epileptic discharge.	96
Figure 16	A page from the EEG of the patient presented in case 4, showing multifocal epileptogenic foci with secondary generalization.	99

Recommendations:

findings

Monitor hcy

Careful use of AEDs in patients

A, but also to the risks associated with hyperhomocysteinemia.

Number	Title	Page
Table 1	Determinants of plasma total homocysteine level	9
Table 2	Total homocysteine level in subjects aged 0-18 years	14
Table 3	Studies of possible mechanisms of vascular damage by hyperhomocysteinemia.	22
Table 4	Studies showing the relationship between CSF-SAM, CSF-Hcy and tHcy, and different neuropsychiatric diseases.	26
Table 5	Mechanisms of neuronal injury caused by homocysteine	27
Table 6	Concentrations of homocysteine and vitamin B6 in plasma, and of vitamin B12 and folate in serum in the study by <b>Schwaninger et al., 1999</b> .	42
Table 7	Conditions that can mimic epileptic seizures.	52
Table 8	ILAE classification of seizures and epilepsy.	55
Table 9	Summary of American Academy of neurology (AAN) evidence-based guidelines levels A or	60

## List of tables

	B recommendation for AEDs use.	
Table 10	A summary of the selection criteria in this study.	65
Table 11	Outline for seizure assessment: Features of a seizure.	67
Table 12	Age distribution of the total patient group and subgroups.	73
Table 13	Sex distribution in the total patient group and subgroups.	73
Table 14	Distribution of patients with positive family history for epilepsy among patient subgroups.	74
Table 15	The seizure severity scale in the total patient group and subgroups.	76
Table 16	Number and percentage of patients with sub-therapeutic, therapeutic or toxic serum levels in the patient subgroups on AEDs.	78
Table 17	Homocysteine level in the total patient group (n=40) and three subgroups.	79
Table 18	Distribution of patients according to EEG findings in the patient group and subgroups.	80
Table 19	Comparison between males and females regarding serum homocysteine level.	81
Table 20	Comparison between patients experiencing different seizure types regarding serum homocysteine level.	82
Table 21	Comparison between patients on monotherapy and polytherapy regarding	83



## List of tables

	serum homocysteine level.	
Table 22	Comparison of patients receiving different types of AEDs monotherapy regarding serum homocysteine level.	84
Table 23	Comparison of patients receiving different combinations of AEDs polytherapy regarding serum homocysteine level.	85
Table 24	The significance of AEDs serum level on homocysteine level in the total patient group.	86
Table 25	Distribution by number and percentage of anti-epileptic drugs number, type and serum level according to seizure type.	89
Table 26	Correlation between age, seizure severity scale, duration of illness and duration of treatment with homocysteine level.	90

## Abbreviations

AAN	American Academy of Neurology
AD	Alzheimer's disease
AEDs	Anti epileptic drugs
A $\beta$	beta-Amyloid
CBZ	Carbamazepine
CK	Creatinine Kinase
CSF	Cerebrospinal fluid
CSF-SAM	Cerebrospinal fluid-S-adenosyl methionine
CSF-tHcy	Cerebrospinal fluid-total homocysteine
DALY	Disability Adjusted Life Years
DTT	Dithiothreitol
EDTA	Ethylene-Diamine-Tetra-Acetate
EEG	Electroencephalogram
ESR	Erythrocyte Sedimentation Rate
GGT	Gamma-Glutamyl Transferase

## Abbreviations

GTC	Generalized Tonic-Clonic
ILAE	International League Against Epilepsy
MBP	Myelin Basic Protein
MRI	Magnetic Resonance Imaging
MS	Multiple sclerosis
MTHFR	Methylene tetrahydrofolate reductase
NIDDM	Non-Insulin Dependant Diabetes Mellitus
NMDA	N-Methyl D-Aspartate
PD	Parkinson's Disease
PHT	Phenytoin
SAH	S-Adenosyl Homocysteine
SAM	S-Adenosyl Methionine
SD	Standard Deviation
SGPT	Serum Glutamic Pyruvic Transaminase
tHcy	Total homocysteine

## ABSTRACT

Epilepsy is a common chronic neurological disorder, which warrants prolonged, and often lifetime, treatment with AEDs. It is commonly associated with hyperhomocysteinemia, a known risk factor for vascular diseases, and which is also related to several other neurological diseases. Homocysteine is an experimental epileptogenic, and nearly 20% of patients with homocystinuria suffer from fits. Hyperhomocysteinemia in epileptic patients is probably related to administration of AEDs.

The aim of our present study is to assess the relationship between treatment with classic anti-epileptic drugs and serum homocysteine level, and to outline the impact of this relationship on patient control and management.

Accordingly we studied 40 patients with the diagnosis of idiopathic epilepsy, who were classified into 3 subgroups; group A which included 10 epileptic patients with newly diagnosed epilepsy or patients on no treatment for at least 6 weeks as a control group, group B which included 15 epileptic patients with controlled seizures and group C which included 15 epileptic patients with uncontrolled seizures. Subjects recruited in the study were subjected to the following: Thorough history taking and neurological examination. Routine laboratory investigations. AEDs serum level determination for patients receiving AEDs. Homocysteine serum level determination. Seizure severity scale estimation. Electroencephalography. Further research: Long term effects of AEDs with or without folate supplementation with respect to seizure control, cardiovascular disease, cognitive performance and mood. Effect of newer AEDs on homocysteine to evaluate their relative safety in cases of feared hyperhomocysteinemia. A prospective study of patients initiating AEDs monotherapy can provide information from intra-patient measurement of homocysteine which can outline the individual AEDs effect on homocysteine.

Keywords:

Serum homocysteine  
Chronic epileptic  
Hyperhomocysteinemia

# *Introduction*

## Introduction:

Elevated concentration of total homocysteine (Hcy) in plasma ( $> 12$  micromol/l) is a risk factor for several diseases of the central nervous system. Epidemiological studies have shown a dose-dependent relationship between concentrations of homocysteine and the risk for neurodegenerative diseases. Homocysteine is a marker for B-vitamin deficiency (folate, B12 and B6). Hyperhomocysteinemia causes hypomethylation which is an important mechanism that links homocysteine to dementia. **(Herrmann et al., 2007)**

The position of epilepsy is more sophisticated, since major anti-epileptic drugs have direct and powerful effects on homocysteine levels, and so the need for follow up of homocysteine levels and the suspicion of its causation in dyscontrol of patients is more justified. **(Apeland et al., 2001)**

Homocysteine is regarded as a neuroexcitatory substance, which is therefore used as an epileptogenic agent in experimental epileptology. Experiments "in vivo" as well as "in vitro" revealed its relation to N-Methyl D-Aspartate (NMDA) glutamate receptors, and its potential neurotoxicity. **(Kolínová et al., 2006)**

AEDs increase serum homocysteine by lowering blood folate levels. Multiple studies have therefore concluded that folic acid supplementation is mandatory in epileptic patients on long term anti-epileptic drugs therapy, with greater stress on children. **(Elliott et al., 2007)**

Hyperhomocysteinemia is present in 15.5% of children receiving long-term AED treatment. Multidrug treatment and long duration of therapy enhance the risk for hyperhomocysteinemia. **(Huemer et al., 2005)**

From the clinical aspect, hyperhomocysteinemia, mostly as a marker of the risk factor in the vascular damage, was often studied in patients treated with antiepileptic drugs. However, the neuroexcitatory influence of mild hyperhomocysteinemia was rarely discussed. **(Kolínová et al., 2006)**

### ***Aim of the work:***

The aim of this study is to assess:

- The relation between treatment with classic anti-epileptic drugs and serum homocysteine level.
- Its impact on patient control and management.