Plasma Level of Homocysteine, Folic Acid and Vitamin B12 Before and After Folic Acid Supplementation in Epileptic Children

Thesis

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By

Hisham Abd El Raouf Gad
M.B.B.CH, Mansoura University
(2002)

Under Supervision of

Prof.Dr. Hamed Ahmed El-Khayat
Professor and Head of Pediatrics Department
Faculty of Medicine – Ain-Shams University

Prof.Dr. Soheir Saad Korraa
Professor of Molecular Biology
National Centre for Radiation Research and Technology
Egyptian Atomic Energy Authority

Dr.Rania Hamed Shatla
Lecturer of Pediatrics
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University

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Hisham Abd El Raouf Gad

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List of Abbreviations

5- HT	:	5 -hydroxy tryptamine
ACTH	:	Adreno cortico trophic hormone
AICARFT	:	5-amino-imidazole-4-carboxamide ribonucleotide transformylase.
AICAR	:	5-aminoimidazole-4-carboxamide ribonucleotide.
AEDs,AED	:	Antiepileptic drugs
ALP	:	Alkaline Phosphatase
ALT	:	Alanin amino transferase
AMPA	:	Amino- 3 hydroxy- 5 methyl- isoxasole propionoic acid
AST	:	Aspartate aminotransferase
ATPase	:	Energy- dependent pump
B12	:	Vitamin b12
Bid	:	Latin word means twice per day
BPEC	:	Benign partial epilepsy with centrotemporal spikes
Ca+2	:	Calcium
CAE	:	Childhood Absence Epilepsy
Cbl	:	Cobolamin
CBS	:	Cystathionine *B*-synthase
CBZ	:	Carbamazepine
CL-	:	Chloride

CPS	:	Complex partial seizures.
CSF	:	Cerebrospinal fluid
CT Scan	:	Computerized tomography
CuZn-SOD	:	Copper-zinc superoxide-dismutase
EEG	:	Electroencephalography
EPSP	:	Excitatory post synaptic glutamate receptors
FBP	:	Folate binding protein
GABA	:	Gamma- amino- butyric acid
GAD	:	Glutamic acid decarboxylase
GART	:	Glycinamide ribonucleotide transformylase
GGT	:	Gamma glutamyl transferase
GPIIb/IIIa	:	Glycoprotein IIb/IIIa receptor
GTC	:	Generalized tonic clonic seizures
HHcy	:	Hyperhomocysteinemia
HIF	:	Log intrinsic factor
HIOMT	:	Hydroxyindole-O-methyltransferase
Hr	:	Hour
Hz	:	Hertz
IBE	:	International Bureau for Epilepsy
ILAE	:	International league against epilepsy
IM	:	Intramuscular
IPSP	:	Inhibitory postsynaptic potential
JME	:	Juvenile myoclonic Epilepsy
K^+	:	Potassium
LEV		Levetiracetam

LGS	:	Lennox gastaut syndrome
M GL u RS	:	Metabotropic glutamate receptors
Mg^{2+}	:	Magnesium
MIR	:	Magnetic Resonance Image
MLT	:	N-acetyl-5-methoxytryptamine
µmol/L	:	Micromole per litre
Mn-SOD		Maganese superoxide-dismutase
MS	:	Methionine synthase
MTS	:	Mesial temporal sclerosis
Na^{+}	:	Sodium
NaOH/KCN	:	Sodium hydroxide/potassium cyanide
NAT	:	N-acetyltransferase
No	:	Number
NO	:	Nitric oxide
PLP	:	Pyridoxal- 5- phosphate
PET	:	Positron emission tomography
PRD	:	Primidone
Qid	:	Latin word means quadruple per day
S		Serum
SAM(AdoMet)	:	S-adenosylhomocysteine
SAH **(AdoHcy)**	:	S-adenosylmethionine
SIADH	:	Syndrome of inappropriate anti-diuretic hormone
SPECT	:	Single photon emission computerized tomography
SRF	:	Sustained high frequency repetitive firing

TCS	:	Tonic-clonic seizures
tHcy	:	Total plasma homocysteine
THF	:	Tetrahydrofolate
Tid	:	Latin word means triple per day
TS	:	Thymidylate synthase
ttt	:	Treatment
u	:	Unit
VPA	:	Valproate
VNS	:	Vagus nerve stimulation

Introduction

Epilepsy, one of the oldest recorded diseases, is a chronic condition characterized by repeated spontaneous seizures. It is considered as one of the most common neurological disorders and represents a major health problem. Structural, metabolic and genetic causes of epilepsy are regularly being identified; however the majority of epilepsies are classified as having an unknown cause ***(Berg et al., 2010).***

Epilepsy is considered as an important neurological disorder affecting 0.3 to 0.5% of population throughout the World causing disability and poor quality of life for patients and their caregivers ***(WHO, 2008).***

An epileptic seizure can be also defined as paroxysmal, transitory disturbance of the brain function that develops suddenly, cease spontaneously and exhibits a conspicuous tendency to recur ***(Frank, 2000).***

Idiopathic epilepsy is epilepsy with no clear cause (other than genetics) in individuals who are neurologically normal apart from there seizures ***(Nelson, 2008).***

Infantile vitamin B12 deficiency leads to ineffective haematopoiesis and degeneration of nervous tissue ***(Alamadan et al., 1993).***

So B12 deficiency may lead to many neurological manifestations as irritability, hypotonia, reflexes abnormalities ***(Graham et al., 1992).***

Vitamin B12 deficiency has been encountered amongst the benign and rare causes of infantile seizures. Common symptoms of Vitamin B12 deficiency in infants include megaloblastic anemia, feeding difficulties, developmental delay, microcephaly, failure to thrive, hypotonia, lethargy, irritability, involuntary movements, seizures and cerebral atrophy ***(Benbira et al., 2007).***

Many causes lead to hyperhomocysteinemia, one of these causes B12 deficiency ***(Soria et al., 1990).***

Homocysteine (Hcy) is a nonessential sulfur-containing amino acid derived from methionine metabolism. The interest of the medical community in this amino acid stems from the observation that elevated plasma Hcy has been associated with cardiovascular disease in multiple large-scale epidemiologic studies and, consequently, it is considered as an independent risk factor for atherosclerosis ***(Humphrey et al., 2008).***

Remethylation of homocysteine requires Vitamin B12 and methyltetrahydrofolate as coenzyme and cosubstrate ***(Boddie et al., 1998).***

Homocysteine is apotential convulsant. It has been described in patients with hereditary defect of Homocysteine metabolism (homocystinuria) and has been suspected as the cause

of increased seizure frequency in these patients ***(Schwaninger et al., 1999).***

The epileptic patients on chronic AED therapy are more prone than the general population to develop hyper-tHcy and low folate levels ***(Tan et al., 2009).***

Hyperhomocysteinemia (Hcy) is defined by plasma Homocysteine concentration greater than 15 mmol/ L ***(Robinson et al., 1996).***

Homocysteine can induce seizures in rats but the exact mechanism remains to be clarified ***(Kubova et al., 1995).***

Although whether the mechanism of the AEDs induces folate depletion is not completely clear. It is suggested that there is an interference with intestinal folate absorption, enzyme activity alteration, folate depletion, and finally interference into the metabolism of the coenzyme forms of folate ***(Elliott et al., 2007).***

Folic acid has been a topic of discussion within the epilepsy community for several decades. Folic acid was initially suspected to be epileptogenic ***(Reynolds et al., 1973).***

Folic acid deficiency is associated with elevated levels of homocysteine, and this phenomenon appears to be prominent in those receiving enzyme-inducing AEDs ***(Schwaninger et al., 1999).*** Homocysteine levels are elevated both at fasting and after methionine loading in persons receiving CBZ, PHT, phenol-barbital (PB), and primidone (PRM) ***(Apeland et al., 2000).***

Belcastro et al. (2007) used a daily folate dose of 5 mg, which was sufficient to normalize, in a population of hyper-tHcy epileptic patients, both plasma tHcy (ranging from 16.6–38 μm) and folate levels (ranging from 3.8–7.5 nm). Given the general agreement that the bioavailability of natural food folate is incomplete, folate fortification has been adopted in the United States, and this strategy should be extended in other countries to minimize the problem. More recently, concern has been raised about possible adverse effects of excessive folate supplementation, which might be harmful in individuals at higher risk, for example, for cancer and cardiovascular disease ***(Sauer et al., 2009).*** Further research is needed to clarify this important aspect.