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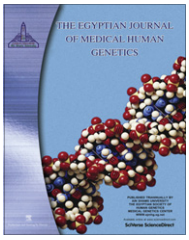

ORIGINAL ARTICLE

Homocysteine, folic acid and vitamin B12 levels in serum of epileptic children

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Abstract The relationship between increased homocysteine (Hcy) level and epileptic seizure remains controversial in human, despite a growing evidence of the pro-convulsive effect of the hyperhomocysteinemia (HHcy) observed in the animal studies. The mechanism of this association with epileptogenesis has not been clearly understood, although there is emerging evidence to support the unfavorable effects of some anti-epileptic drugs (AEDs) on the plasma homocysteine (Hcy) concentrations. The aim of this study was to uncover the relationship between the levels of homocysteine (Hcy), the cofactors involved in its metabolism as folic acid and vitamin B12 and anti-epileptic drugs (AEDs) in epileptic patients. Serum level of homocysteine (Hcy), folic acid and vitamin B12 was measured in 60 patients with idiopathic epilepsy; and its level was compared to 30 healthy children serving as control group. No significant difference was found regarding the plasma homocysteine (Hcy) levels between patients (both receiving anti-epileptics and non anti-epileptic drug users) and controls. Epileptic patients on polytherapy showed higher mean serum levels of homocysteine (Hcy) and lower mean serum levels of folic acid compared to those on monotherapy. However, the mean serum levels of homocysteine (Hcy), vitamin B12 and folic acid showed non significant differences between patients using valproic acid (VPA) or carbamazepine (CBZ). Duration of AED therapy showed a significant positive correlation with mean serum levels of homocysteine (Hcy) and a significant negative correlation with mean serum levels of folic acid. To conclude;

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AEDs upset the homeostatic balance of homocysteine (Hcy) and its cofactors and cause abnormalities in their serum levels.

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1. Introduction

Homocysteine (Hcy), is a sulfur-containing amino acid that is formed by de-methylation of methionine [1]. Plasma Hcy concentrations vary with ethnic background, increase with age, are higher in adult men and postmenopausal women, and lowest in children [2]. In children, hyperhomocysteinemia (HHcy) is defined according to age and (after puberty) sex-specific percentiles [3].

Folic acid and vitamin B12 have roles in the metabolism of Hcy and defects in the metabolism of any of them may lead to increased serum Hcy levels, resulting in atherosclerosis [4,5].

It has been reported that Hcy induces neuronal cell death by stimulating N-methyl D aspartate (NMDA) receptors mediating excitotoxicity, as well as by producing free radicals [6] and induction of apoptosis [7]. Its metabolites, homocysteic acid and L-Hcy sulfinic acid, also exhibit high excitotoxic potency by interacting with different glutamate receptor subtypes [8]. They are potent agonists of the NMDA-type glutamate receptor, which are linked with epileptogenesis [9].

Also, stimulation of NMDA receptors by Hcy with excessive calcium influx causes reactive oxygen generation and neurotoxicity that contribute to the cognitive changes and the marked increased risk of cerebrovascular disease in children and young adults with homocysteinuria. In addition, disruption of blood–brain barrier (BBB) in patients with stroke and HHcy exposes the brain to near plasma levels of Hcy and increases neurotoxicity [6].

In animals, systemic administration of high doses of Hcy produces convulsive seizures, a fact that has been exploited in models of experimental epilepsy [10]. Furthermore, there are some data from animal studies demonstrating that Hcy sequesters adenosine, an endogenous anticonvulsant, and thereby reduces the seizure threshold [11].

Therefore, Hcy through these mechanisms, may reduce seizure threshold and increase seizure frequency in patients treated with AEDs. Other mechanisms, such as oxidative stress, DNA damage, inhibition of NA/K-ATPase and activation of caspases, could be involved in Hcy-induced neuronal excitotoxicity [12].

There is little information on the influence of antiepileptic drugs on Hcy levels in pediatric patients. HHcy was reported in 15.5% of children receiving AEDs [13]. Little is known on how phenytoin (PHT), valproic acid (VPA) and carbamazepine (CBZ) exert their effect on Hcy metabolism. It has been suggested that enzyme inducers, can directly modulate the activity of different liver enzymes which in turn may cause depletion of the cofactors involved, leading to the alternations observed in Hcy status [13].

In fact, an independent predictor of HHcy in patients treated with PHT or CBZ is the presence of a homozygous thermolabile genotype of 5,10 methyl tetrahydrofolate reductase (MTHFR), suggesting a gene–drug interaction as a cause of HHcy, this hypothesis is supported by Ono et al. [14]. Additionally, increased Hcy and low folate status may contribute to the development of AEDs related side effects, such as impaired cognitive function, and fetal malformation [15].

The aim of this study was to uncover the relationship between the levels of Hcy and the cofactors involved in its metabolism as folic acid and vitamin B12 and AEDs in epileptic patients.

2. Subjects and methods

2.1. Subjects

This study was a cross-sectional study, conducted on 60 epileptic children diagnosed with idiopathic epilepsy according to the guidelines of The Classifications of the International League Against Epilepsy (1998) [16], with age ranging from 5 to 15 years old. They were recruited from the Pediatric Neurology outpatients' clinic of Children's Hospital, Ain Shams University.

Patients were divided into two groups: Group (I), comprised 20 newly diagnosed epileptic children not receiving anti-epileptic medication (non-AED users). Group (II), comprised 40 epileptic children on regular antiepileptic medication for at least one year (AED users). Group II was further subdivided into: Subgroup (A) which comprised 20 epileptic children receiving monotherapy. Therapy consisted of either valproic acid (VPA) or carbamazepine (CBZ). VPA group comprised 12 children and CBZ group comprised 8 children. Subgroup (B), receiving polytherapy treatment (combined treatment with VPA and CBZ) comprised 20 patients. Serum concentrations of both VPA and CBZ were maintained within the therapeutic range throughout the study (71.4 ± 13.09 μg/ml and 7 ± 1.9 μg/ml, respectively).

Thirty non-epileptic children of the same age and sex as patients served as controls. Children with diseases affecting the serum level of Hcy as endocrinal, liver, kidney and cardiac diseases, diabetes mellitus and nutritional deficiencies or those receiving vitamin supply or folic acid antagonists as well as the vegetarians were excluded from the study. Moreover, patients with uncontrolled seizures were excluded from the study to limit the variables and to make sure not to change the dose of AEDs throughout the study.

2.2. Methods

After obtaining the approval of the Ethics Committee at the Pediatric Hospital, Ain Shams University, consents for participating in the study were signed by the parents or caregivers. Children were subjected to the following: Detailed history laying stress on age of onset of seizure, milestones of development, symptoms of neurological deficits as well as symptoms suggestive of an underlying etiology (according to the commission on Epidemiology and Prognosis, International League against Epilepsy, 1989) [16], type of seizure disorder (according to the recommendations of the International League against Epilepsy, 1981) [17] and duration of the disease. Care should

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