Assessment of Serum Homocysteine Level in Epileptic Patients on Carbamazepine Treatment

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Abstract:

Background: *This comparative cross sectional study was carried out to evaluate the level of serum homocysteine with carbamazepine treatment in epileptic patients.*

Materials and Methods*: This study was conducted in the Department of Neurology, BSMMU, Dhaka, from March 2013 to December 2015 for the duration of two years and nine months period. Patients, who were diagnosed as epileptic and receiving Carbamazepine at least for six months and no other anti epileptic drugs (AEDs), were considered as case group and Patients other than epilepsy attending Neurology outpatient department (NOPD) were considered as control group.*

Results: *A total of 104 patients were recruited as study population. Of them 52 patients grouped into case and the rest 52 patients in control. The mean (SD) value of serum homocysteine in epileptic patients using carbamazepine as anti-epileptic drugs found 16.33 (5.34) ¼mol/L which was highly statistically significant difference than control group measuring 8.77 (3.75) ¼mol/L. Considering the normal level 5- 15 ¼mol/L, in epileptic patients with carbamazepine therapy, increased level was found in 53.8% patients. On the other hand, in control group, 13.5% had increased value of serum homocysteine.*

Conclusion: *Carbamazepine therapy which is usually given to epileptic patients may interfere with metabolic pathways of homocyateine (Hcy) as well as may lead to an alteration of its serum levels.*

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Introduction:

Many developing countries such as Bangladesh, India are are densely populated. Like tuberculosis, malaria epilepsy is also a burden for our country. Anti- epileptic drugs are commonly used to treat epilepsy.

Commonly used first-generation antiepileptic drugs- carbamazepine, sodium valproate, phenytoin and phenobarbitone. Second-generation antiepileptic drugs are- lamotrigine, gabapentin, topiramate etc. Oxcarbazepine and levetiracetam- available but are highly expensive

However consumption of carbamazepine causes significant elevation of serum homocysteine level[1] .

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Elevated serum homocysteine (Hcy) is responsible for ischaemic heart disease, deep vein thrombosis, pulmonary embolism and stroke[2]. Near about 10-40% of epileptic patients develop hyperhomocysteinaemia[3]. High plasma homocysteine is an independent risk factor for cardiovascular disease and thrombosis[4]. Anti-epileptic drugs raise serum homocysteine (Hcy) by reducing blood folate levels[5].

Atherosclerotic vascular diseases are associated with well-known risk factors such as systemic arterial hypertension, diabetes mellitus, smoking and obesity, but in the last decade other emerging risk markers have been identified, one of them is being Hcy. Atherosclerosis is a chronic inflammatory disease of the blood vessel walls, in which deposits of lipids, cholesterol, calcium and other substances build up in the endothelial layer of the arteries. Many studies have identified moderate elevation of serum Hcy as an independent risk factor for atherosclerotic vascular disease[6].

Lowering of serum folate and elevation of Hcy concentrations in blood are associated with poor cognition in general population. High levels of Hcy result in neurotoxic and vasotoxic effects in dementia and Alzheimer's disease, suggesting that Hcy is a direct marker of early cognitive deficit[7].

The pathogenic role of high serum Hcy is in vascular dementia is yet no clear. The levels of serum Hcy, vitamin B12 and plasma folate were studied in Alzheimer's disease and vascular dementia, and it was found that Hcy was increased, while vitamin B12 and folic acid were decreased in both of these conditions. This suggests that supplementation of vitamin B12 and folate may be beneficial in vascular dementia and Alzheimer's disease [8].

Materials and Methods:

This study was conducted in the Department of Neurology, BSMMU, Dhaka, from March 2013 to December 2015 for the duration of two years and nine months period. Cases were selected by simple random sampling. Age ranges of the patients were 14 to 60 years. Because baseline serum Hcy level have similarity in these age group. Moreover we have collected cases from epilepsy clinic of adult neurology. Epileptic patients with other systemic diseases such as: Chronic kidney disease, Hypothyroidism, chronic liver disease, Leukemia, Inflammatory bowel disease, psoriasis and homocysteinuria were excluded from this study[9]. Patient with Diabètes Mellitus, Smoking, Pregnancy, age less than 14 years and greater than 60 years, taking Methotrexate, Isoniazide or other AEDs ,folic acid supplement, receiving vit-B6, Vit- B12 or on folate antagonists were also excluded from this study

Data were collected by a pre-designed proforma. Detailed history and clinical examination were carried out and structured questionnaire were used to collect the necessary information. Similar numbers of controls were also selected. Relevant base line investigations were done which included Complete blood count with peripheral blood film where applicable, Urine R/M/E, Serum creatinine, ALT,Thyroid function tests in suspected hypothyroidism.

Serum Hcy assay was done from venous blood of both cases and control in the Department of Biochemistry, BSMMU on the day of sample collection. The ARCHITECT Homocysteine assay, a chemiluminescent micro particle immunoassay (CMIA) technology was used to measure homocysteine value. Statistical analysis of data was carried out with appropriate techniques and systems.

Results:

A total of 104 patients were recruited as study population. Of them 52 patients grouped into case and the rest 52 patients in control.

Table-I

Distribution of patients (Case group) according to epilepsy type (n= 52)

Type of Epilepsy	Frequency (n)	Percentage
Simple partial	17	32.7
Complex partial	5	9.6
Primary generalized	26	50.0
Secondary generalized	4	7.7

This table I shows distribution of Case group patients according to epilepsy type. Here, half of the patients, 50% had primary generalized epilepsy which was followed by simple partial type 32.7%. Complex partial was accounted 9.6% whereas secondary generalized 7.7%.

Table-II

Distribution of case group patients according to duration of diagnosis and treatment (n=52).

Duration (Years)	Mean	SD
Duration of diagnosis	4.29	4.51
Duration of treatment	4.05	3.59

This table II shows distribution of case group patients according to duration of diagnosis and treatment. The mean (SD) value of duration of diagnosis was 4.29 (4.51) years while duration of treatment was 4.05 (3.59) years.

Table-III

Distribution of case group patients according to Carbamazepine dose level (n=52)

Carbamazepine dose (per day)	Frequency (n)	Percentage
200 mg	2	3.8
400 mg	18	34.6
800 mg	30	57.7
1000 mg	2	3.8

This table III shows distribution of case group patients according to Carbamazepine dose level. Out of all patients, 57.7% patients were taken 800 mg carbamazepine daily. The second highest portion of patients 34.6% was taken 400 mg of carbamazepine daily.

Table-IV

Distribution of patients according to serum level of homocysteine (N=104)

Type of Patients	Serum Homocysteine (micro mol/L)		p-value*
	Mean	SD	
Case	16.33	5.34	<0.0001[s]
Control	8.77	3.75	

S=significant

* P-value derived from independent sample t test

Table IV: shows distribution of patients according to serum homocysteine level. The mean (SD) value of serum homocysteine in epileptic patients using carbamazepine as anti-epileptic drugs found highly increased than control group [16.33 (5.34) vs. 8.77 (3.75)]

Table-V

Distribution of patients according to range of serum Homocysteine level (N=104).

Type of Patients	Serum Homocysteine (¼mol/L)	
	Minimum	Maximum
Case	8.45	30.28
Control	5.30	19.00

The table II shows distribution of patients by range of serum homocysteine level. Here, in case group, the range was 8.45 to 30.28 ¼mol/L and that of 5.30 to 19.00 ¼mol/L in control group

Discussion:

Carbamazepine (CBZ) is a potent antiepileptic drug. It is commonly used in partial onset and secondary generalized seizures. It has also good efficacy in the treatment of primary generalized tonic-clonic seizures. Some studies showed in epileptic patients receiving CBZ, there is significant elevation of serum homocysteine levels[10]. No previous study has done in Bangladeshi subjects. It is one of the foremost studies of epilepsy patients taking carbamazepine therapy to consider their serum homocysteine level in Bangladesh context. We compared our study findings with result of some other published articles elsewhere in the world.

According to gender distribution, no statistically significant difference was observed between two groups. Out of all patients, 67.3% were male and 32.7% female in carbamazepine treated patients. In control group patients, 63.5% was male and 36.5% female.

In analysis of epilepsy type, half of the patients, 50% had primary generalized epilepsy which was followed by simple partial type 32.7%. Complex partial was accounted 9.6% whereas secondary generalized 7.7%.

The mean (SD) value of duration of diagnosis was 4.29 (4.51) years while duration of treatment was 4.05 (3.59) years. Out of all patients, 57.7% patients were taken 800 mg carbamazepine daily. The second highest portions of patients 34.6% were taken 400 mg of carbamazepine daily.

The present study showed that epileptic patients receiving carbamazepine as AEDs have increased serum levels of homocysteine. The mean value of serum homocysteine in epileptic patients taking carbamazepine as anti-epileptic drugs found 16.33 (5.34) ¼mol/L which was highly statistically significant difference than control group measuring 8.77 (3.75) ¼mol/L. However, in case group the highest number of 13 patients had their value in 15 – 20 ¼mol/L and highest value 30 ¼mol/L had only in 1 patient. At the same time, in control group highest number of 21 patients had their value in 5 – 10 ¼mol/L and highest value near about 20 ¼mol/L had in 2 patients. In case group, the range of serum homocysteine was found 8.45 to 30.28 ¼mol/L and that of 5.30 to 19.00 ¼mol/L in control group.

Our results are in consistent with the previous reports on homocysteine concentrations in patients with epilepsy taking AED specially CBZ. Paknahad et al, also recorded mean of serum Hcy concentration in epileptic patients receiving CBZ was significantly higher compared to that in the controls [13.66 (0.95) vs. 12.97 (0.46) ¼mol/L, p = 0.04][4]. The similar result was obtained if patients with only CBZ monotherapy were included, Minitzer et al, found 11.1 (4.2) ¼mol/L[11] . Epilepsy patients switching from the enzyme inducing AEDs, phenytoin or CBZ to the non inducing AEDs drugs, LTG or levetiracetam results in significant declines in serum homocysteine level.

Conclusion:

In conclusion, our data demonstrate that serum homocysteine level significantly increased in carbamazepine treated epileptic patients. Therefore,

it should be monitored the level of homocysteine in epileptic patients and managed accordingly.

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