The effects of antiepileptic drugs (AED) on serum copper level in children with epilepsy.

Abstract

Background: Epilepsy is a central nervous system disorder in which brain activity becomes irregular, causing seizures or periods of unusual behavior, sensations, and sometimes loss of awareness. Long term use of antiepileptic drugs may alter serum copper level.

Objective: The purpose of the present study was to assess the serum copper level in childhood epilepsy treated with long-term Anti Epeleptic Drug (AED)

Methodology : This cross-sectional study was carried out in the outdoor and indoor patient department of Paediatric Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU) during the period from March' 2013 to August' 2013. Sample size was one hundred, among these fifty was case e.g. epileptic child who had received anti-epileptic drugs (Carbamazepine and/or Valproic acid) for more than three months and fifty was e.g. newly diagnosed epileptic child, who have not yet received antiepileptic drugs.

Result: In this study, among 100 epileptic child, mean copper level in case group was 1.11(±0.32) (µg/ml) and in control group was 0.96(±0.20) (µg/ml), which was statistically significant ($p<0.05$).

Conclusion: The use of one drug or multiple drugs in the treatment of epileptic patients has made serum level of copper significantly higher.

Keywords : serum copper, childhood, epilepsy, antiepileptic drug, long-term

Introduction: Epilepsy is a recurrent, unprovoked, seizure manifested by an abnormal and excessive synchronized discharge of a set of cerebral neurons. The discharge results in almost instantaneous disturbance of sensation, loss of consciousness or convulsive movements or some combination of the above characteristic.[1] Epilepsy is one of the most common neurological diseases with a prevalence rate varying from 2.8 to 19.5 per 1000 general population and it prevails more specially among school children.[1,2,3,4] In Bangladesh it is estimated that there were at least 1.52 million people with epilepsy. In a community based survey at Dasher Kandi in Bangladesh, it was found that incidence of epilepsy was 2.54 per 1000 Population.[5] Over two-thirds of all epileptic seizures begin in childhood (most in the first year of life) and this is the age period when seizures assume the most array of forms[6].Trace elements (e.g. Copper, Zinc and Manganese) are minor building components in tissues including the nervous system. The very complex balance of trace elements is crucial for all areas for maintaining human health, preventing as well as overcoming health problems[7]. Trace elements play important functional roles in peripheral and central nervous systems[8-13]. Zinc, selenium, and copper are indispensable components for certain enzymes (such as glutathione peroxidases) responsible for various metabolic processes in different tissues including the brain[14].

Copper (Cu^{++}) is involved in number of enzymes which catalyzes and oxidizes many reactions. Some studies reported relationship between the serum levels of Cu^{++} and Zn^{++} and CuZn-SOD activity and the serum concentration of Se^{2+} and GSH-Px activity in the group of healthy subjects[21]. Crl (a copper-binding protein) appears to have two antioxidant properties: firstly, it binds Cu^{++} and therefore prevents this transition metal from catalyzing hydroperoxide decomposition to radicals. Secondly, Crl oxidizes ferrous iron to ferric and concomitantly converts O_2 to H_2O, thereby inhibiting iron-dependent lipid peroxidation[22].

Deficiency or excess amount of these trace elements play role in several well recognized diseases[24], Studies are going on to establish their role in epilepsy. Anti-epileptic drugs alter metabolism and distribution of blood trace elements like Copper. Sözüer et al measured serum copper (Cu) levels in 52 epileptic children who were treated with either Carbamazepine (CBZ) or Valproic acid (VPA) or with a combination of CBZ and VPA. Combination therapy and monotherapy with CBZ increased serum Cu levels. No significant alteration in serum Cu levels was observed with VPA monotherapy.[26]

Symptoms of excess copper include pain in the abdomen, nausea, vomiting, diarrhea, fatigue, premenstrual syndrome, anorexia, depression, anxiety, migraine headaches, jaundice and many others.[30] Excessive copper in children is associated with hyperactive behavior, learning disorders such as dyslexia, ADD and infections such as ear.[31]The aim of the study was to assess the serum copper level in childhood epilepsy treated with long-term Anti Epileptic Drug (AED).

Methodology: This cross-sectional study was carried out in the outdoor and indoor patient department of Paediatric neurology, BSMMU during the period from March' 2013 to August' 2013. Sample size was one houndred, among these fifty was case e.g. epileptic child who had received anti epileptic drugs (Carbamazepine and/or Valproic acid) for more than three months and fifty was control e.g. newly diagnosed epileptic child, who have not yet received antiepileptic drugs. Clinically diagnosed patient of epilepsy from 1 month to 18 years of age and treated with Carbamazepine and/or Valproic acid ≥ 3months were included in this study. Epileptic children with other systemic illnesses such as diabetes, renal failure, malnutrition or any infectious diseases and receiving antiepileptic drug for less than three months or receiving antiepileptic drug other than studied drugs were excluded from this study. Sample was selected by non random sampling method. After proper selection of case & control complete history was taken from accompanying attendants. Through clinical examination was done. Relevant investigation reports were collected and recorded. Serum copper (Cu) were measured by atomic absorption spectrophotometer[17].The name of spectrophotometer is graphite furnance atomic absorption spectrophotometer (GF-AAS, 6650, Shimadzu: KYOTO, JAPAN) and analysis was done in biochemistry laboratory of BSMMU(Bangabandhu Sheikh Mujib Medical University) and ICDDR,B.(International Centre for Diarrhoeal Diseases Research, Bangladesh. After collecting all the data, analysis has been done by using SPSS and the results are displayed in tables and diagrams. Discussions have been done by comparing the results of the study with the results from similar study done by others.

Result:

A total number of 100 children were enrolled for this study, out of which 50 were case and 50 were control. Mean age of study population was 4.39 (±2.34) years whereas case group was 4.08 (±2.21) years and control group was 4.70 (±2.45) years.

Table 1: Age group distribution of the study population

	Study group		
Age group	Case/Epileptic	Control	Total
1-2 years	16 (32%)	14 (28%)	30
>2 to 5 years	21 (42%)	16 (32%)	37
>5 years	13 (26%)	20 (40%)	33
Total	50 (100%)	50 (100%)	100
Mean ±SD	4.08(±2.21)	4.70(±2.45)	4.39(±2.34)

Amoung the study population male female ratio was 1.63:1.

Table 2: Sex distribution of the study group

	Study group		
	Epileptic	Control	Total
Male	31	31	62
Female	19	19	38
Total	50	50	100

Socio-economic status of the study population shows that, two-thirds 62% patients were from middle class, 23% were from lower socio-economic group and 15% were from upper socio-economic group.

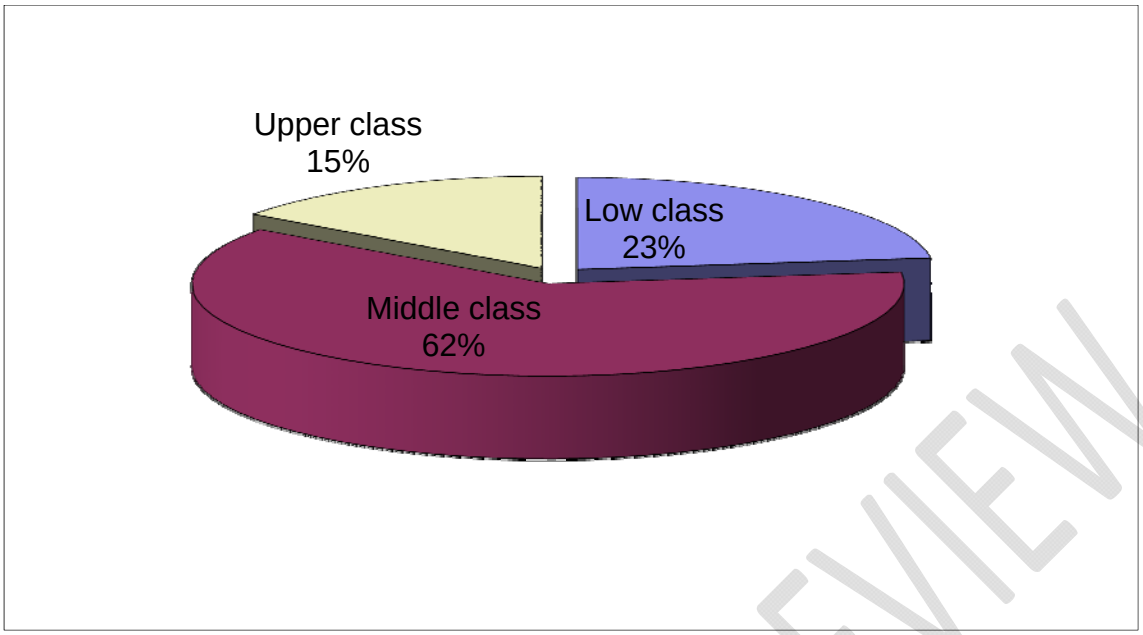

Figure I: Socio-economic status of the study population.

Table 3: Family history of epilepsy of the study group

Family H/O Epilepsy	**Study group**			
	Epileptic n (%)	Control n (%)	**Total**	**P value**
Yes	17(34)	08(16)	25	0.001
No	33(66)	42(84)	75	
Total	50(100)	50(100)	100	

Here, calculate the P value by using Chi-square test.

By the study on family history of epilepsy, it was found that , in epileptic group 34% had family history of epilepsy and in control group 16% had family history of epilepsy and that was statistically significant ($p<0.05$).

Table 4: Character of seizure of the study population

Character of seizure	**Study group**			
	Epileptic n(%)	Control n(%)	**Total**	**P value**
Generalized tonic clonic	39(78)	36(72)	75	**0.57**
Tonic	06(12)	08(16)	14	
Clonic	03(06)	04(08)	07	
Others	02(04)	02(04)	04	

Here, calculate the P value by using Fisher's exact probability test.

It was found that , generalized tonic clonic seizure were 78% in epileptic group and 72% in control group. Tonic seizure were 12% in epileptic group and 16% in control group. Clonic seizure were 06% in epileptic group and 8% in control group which were not statistically significant (p>0.05)

Table 5 : EEG findings of the study population

EEG findings	**Study group**			
	Epileptic n(%)	Control n(%)	**Total**	**P value**
Generalized seizures	32(64)	27(54)	59	**0.30**
Focal seizure	18(36)	23(46)	41	
Total	50(100)	50(100)	100	

Here, calculate the P value by using Chi-square test.

Study on EEG findings, it was found that generalized seizure in epileptic group were 64% were and in control group were 54% . Focal seizure in epileptic group were 36% and in control group were 46%, where (p>0.05) had not statically significant.

Table 6: Mean difference of serum copper level of the epileptic group and control group.

	Study group		
	Epileptic	Control	P value
Cu (µg /ml)	1.11(±0.32)	0.96(±0.20)	0.03

Here, calculate the P value by using unpaired "t" test.

Mean copper level was 1.11(±0.32) (µg/ml) in epileptic group and 0.96(±0.20)(µg/ml) in control group, where ($p<0.05$) that was statistically significant .

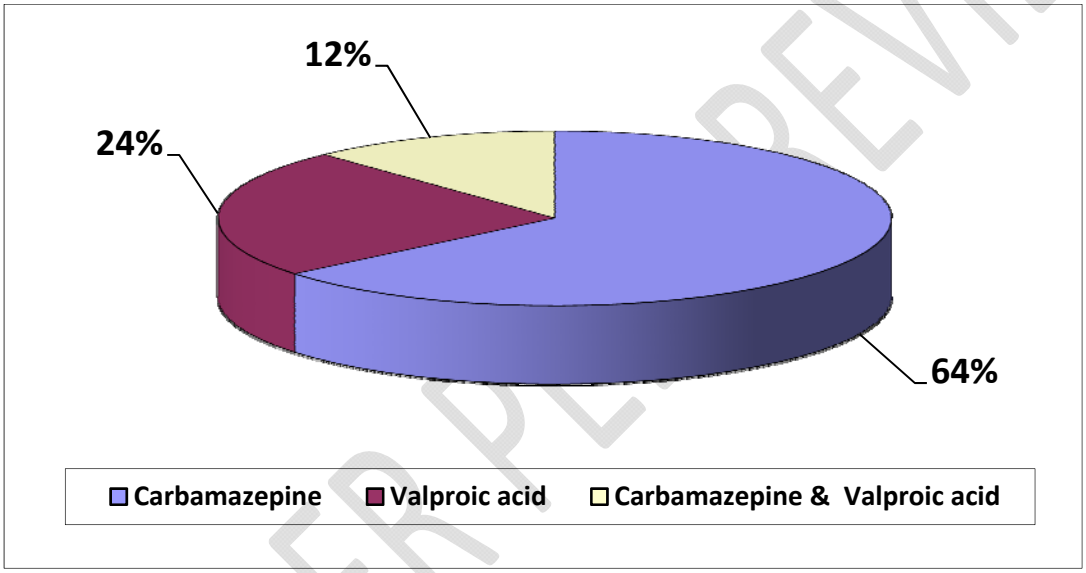

Figure II: Type of usage of anti-epileptic drug

Figure shows: Two thirds (64%) patients were given carbamazepine therapy, 24% were given valproic acid therapy and 12% carbamazepine and valproic acid both in this study.

Table 7: Mean Cu (µg/ml) level between different anti epileptic drugs

	Epileptic patients			
	Carbamazepine	Valproic acid	Carbamazepine and Valproic acid	P value
Cu (µg /ml)	1.24(±0.36)	1.02(±0.21)	1.09 (± 0.39)	0.04

Here, calculate the P value by using "One way ANOVA test". It was done by SPSS software version - 17. In multiple comparisons in between three drugs group ($p<0.05$) were significant.

After medication with carbamazepine(CBZ), valproic acid(VPA), carbamazepine and valproic acid(CBZ+VPA) mean copper levels were 1.24(±0.36) (µg/ml), 1.02(±0.21) (µg/ml) and 1.09 (± 0.39) (µg/ml) respectively which was found statistically significant ($p<0.05$).

Discussion:

Childhood epilepsy is a worldwide problem. Trace elements (e.g. Copper, Zinc and Manganese) are minor building components in tissues including the nervous system. This study has been designed to determine the levels of copper (Cu) in serum from patients with epilepsy in children who were taking anti-epileptic drugs (carbamazepine and/or valproic acid) for at least three months. This was a cross-sectional study among the patients who were consulted and admitted at the department of Paediatric neurology, BSMMU. In this study mean age was 4.39(±2.34). In epileptic group mean age was 4.08(±2.21) and control group was 4.70(±2.45). As compared with Tekin et al.[21] study mean age group was 4.24(±0.35) and case group was 4.69(±1.12) that result was approximately similar to our study. Another study by Saboktakin et al [24] also corroborates with our study. Diop et al's study in Senegal [25] was limited to children aged between 1 to 9 years.

In this study sex distribution of epileptic group and control group have shown male female ratio was 1.63:1. A study by Nouri et al demonstrated that male-to-female ratio was 1.75:1.These results corroborate with our study.[26]

In this study, epileptic group had 34% family history of epilepsy and in control group 16% had family history of epilepsy and that was statistically significant ($p<0.05$). Saboktakin et al demonstrated that the family history of epilepsy were positive in 9% of epileptic patients.[24]

In this study, 78% generalized tonic clonic seizures were in epileptic group and 70% were in control group. Tonic was 12% in epileptic group and 16% in control group. Clonic was 06% in epileptic group and 8% in control group, which was not statistically significant ($p>0.05$).

Ogunlesi T et al reported that generalized tonic-clonic seizures were the commonest seizure type of their study (97; 76.9%). These were followed by tonic seizures (8; 6.3%), clonic seizures (6; 4.8%) and myoclonus (3; 2.4%) [27] that match with this present study.

Following the clinical diagnosis of epilepsy in an individual Osuntokon B O et al demonstrated that it was usually recommended an EEG, amongst other investigations, be carried out. The EEG provides three types of information: confirmation of an abnormal electrical activity; information about the type of seizure disorder and the location of the seizure focus.[28,29] In this present study EEG findings, generalized seizure activity was 64% in epileptic group and 54% in control group. Focal seizure was 36% in epileptic group and 46% in control group and those results were not statistically significant ($p>0.05$). However, Meindari H et al conducted a EEG-based studies of epilepsy to show the frequency of seizure type. According to their literature, generalized seizures account for 45% of all seizure types, whereas focal seizures are present in 55% of cases. [30] It is crucial to recognize that a normal EEG does not exclude epilepsy, as around 10% of patients with epilepsy never show epileptiform discharges. Secondly, an abnormal EEG demonstrating IED (interictal epileptiform discharge) does not in itself indicate that an individual has a seizure disorder, as IED are seen in a small percentage of normal subjects who never develop epilepsy and IED may also be found in patients with neurological disorders which are not complicated by epilepsy.[31,32.]

In this present study mean copper level was 1.11(±0.32) (µg/ml) in epileptic group and 0.96(±0.20)(µg/ml) in control group, where ($p<0.05$) that was statistically significant .Studies of Saboktakin et.al.[24], Barbeaus et.al.[23] and Verrotti et.al [22] have also corroborated with the similar results of our study on serum copper levels in epileptic patient under drug therapy. Saboktakin et al demonstrated that the mean copper level in patients with epilepsy under drug treatment was

1.06 (± 0.36) µg/ml and in control group was 0.93 (± 0.25) µg/ml, which was significantly higher in the case group. Although their control group were normal healthy subjects. Besides this, Verrotti's et al. [22] have demonstrated no significant difference in the levels of other elements (copper and magnesium).

After medication with carbamazepine(CBZ),valproic acid(VPA), carbamazepine and valproic acid(CBZ+VPA) mean copper levels were 1.24(±0.36) (µg/ml), 1.02(±0.21) (µg/ml) and 1.09 (± 0.39) (µg/ml) respectively which was found statistically significant ($p<0.05$). Here we observed that monotherapy with CBZ has lead to more potentiality to increase serum copper levels as compared with combination therapy (CBZ+VPA) or VPA alone.

Studies of Sherifa et.al.[33], Sözüer DT[26] et al have also corroborated with the similar results with our study on serum copper levels in epileptic patients. Sherifa and colleagues demonstrated that serum levels of copper in patients with epilepsy on treatment (particularly with sodium valproate and carbamazepine) were high.[33]

In Sözüer DT et al [26] demonstrated that the serum level of copper in patient's under treatment by carbamazepine and valproate sodium was significantly higher. In their study copper levels were 0.27 ± 0.10(µg/ml) and 1.11 ± 0.35(µg/ml) respectively in patients treated with carbamazepine and 0.35 ± 0.15(µg/ml) and 0.99 ± 0.36 (µg/ml) respectively in patients treated with sodium valproate. That results were showed combination therapy and monotherapy with CBZ increased serum Cu levels ($p < 0.05$). Liu demonstrated that antiepileptic treatment is associated with elevated serum copper level and ceruloplasmin.[34]

Conclusion: The use of one drug or multiple drugs in the treatment of epileptic patients has made significant differences in the levels of serum copper. The serum level of copper in patient under treatment with carbamazepine and/or valproic acid was significantly lower.

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