Journal of Pharmaceutical Research International

27(2): 1-7, 2019; Article no.JPRI.48415
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

The Effects of Antiepileptic Drugs (AED) on Serum Copper Level in Children with Epilepsy

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Authors' contributions

This work was carried out in collaboration among all authors. Author SAS designed the study, wrote the protocol and the first draft of the manuscript. Authors HR and IJ managed the analyses of the study and literature searches. Author MRA performed the statistical analysis and contributed in final manuscript writing. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2019/v27i230166
Editor(s):
(1) Dr. Vasudevan Mani, College of Pharmacy, Qassim University, Buraidah, Kingdom of Saudi Arabia.
Reviewers:
(1) Ufuoma Bigila Shemshere, Federal University Birnin Kebbi, Nigeria.
(2) Shigeki Matsubara, Jichi Medical University, Japan.
Complete Peer review History: http://www.sdiarticle3.com/review-history/48415

Original Research Article

Received 09 February 2019
Accepted 20 April 2019
Published 08 May 2019

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. Serum copper level may change due to long term use of antiepileptic drugs.
Objective: The purpose of the present 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 Department of Paediatric Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU) during March to August' 2013. Sample size was one hundred, among these fifty were case (epileptic child who had received anti-epileptic drugs (Carbamazepine and/or Valproic acid) for more than three months) and rest fifty were control (newly diagnosed epileptic child, who yet not received antiepileptic drug).
Result: The mean copper level was 1.11±0.32 µg/ml in case group and 0.96±0.20 µg/ml in control group, which was statistically significant ($p<0.05$).
Conclusion: The use of one drug or multiple drugs in the treatment of epileptic patients may play significant role in increasing copper serum level.

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Keywords: Serum copper; childhood; epilepsy; antiepileptic drug; long-term.

1. 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]. Different mineral elements are perilous for usual working of the central nervous system, and some studies have established that changes in different electrolytes of the body, such as sodium, potassium, magnesium, and the trace elements such as copper (Cu) and zinc (Zn) subsequently are effective on the incidence of convulsions and epilepsy [5]. The routine treatment of the epilepsy is using anticonvulsant agents. The use of such drugs mainly controls the disease, or can reduce the times of the seizure. After initial recognition, approximately 70% of patients have controlled seizures with antiepileptic drugs (AEDs). Approximately 25% of patients with epilepsy do not have any observed improvement in the reduction of the amount of seizures, even when 2 or 3 AEDs are used. Some studies have shown the importance of a specific diet, hormones, and micronutrients in the management of patients with epilepsy [6].In Bangladesh it is estimated that there were at least 1.52 million people with epilepsy. In a community based survey in Bangladesh, the incidence of epilepsy was found 2.54 per 1000 Population [7]. 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 [8]. 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 [9]. Trace elements play important functional roles in peripheral and central nervous systems [10-13]. 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 catalizes 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 Se2+ and GSH-Px activity in the group of healthy subjects [15]. Crl (a copper-binding protein) appears to have two antioxidant properties: Firstly, it binds Cu++ and therefore prevents this transition metal from catalyzing hydroperoxidedecomposition to radicals. Secondly, Crl oxidizes ferrous iron to ferric and concomitantly converts O2 to H2O, thereby inhibiting iron-dependent lipid peroxidation [16].

Deficiency or excess amount of these trace elements play role in several well recognized diseases [17], 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 [18].

Symptoms of excess copper include pain in the abdomen, nausea, vomiting, diarrhea, fatigue, premenstrual syndrome, anorexia, depression, anxiety, migraine headaches, jaundice and many others [19]. Excessive copper in children is associated with hyperactive behavior, learning disorders such as dyslexia, ADD and infections such as ear [20]. The aim of the study was to assess the serum copper level in childhood epilepsy treated with long-term Anti Epileptic Drug (AED).

2. METHODOLOGY

This cross-sectional study was carried out in the Department of Paediatric Neurology, BSMMU during March 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 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 as case. 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 and control complete history was taken from accompanying attendants. After through clinical examination, relevant investigation reports were collected and recorded. Serum copper (Cu) were measured by atomic absorption spectrophotometer (GF-AAS, 6650, Shimadzu: KYOTO, JAPAN) [21] at the 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.

3. RESULTS

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.

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.

Table 1. Age group distribution of the study population

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

Among the study population male female ratio was 1.63:1

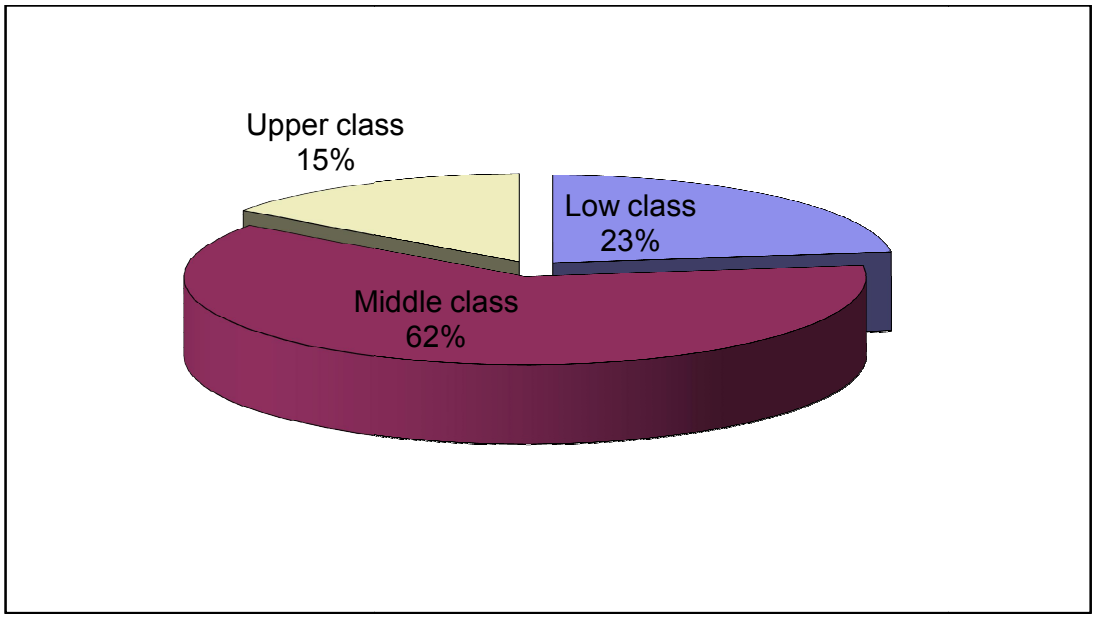

Fig. 1. Socio-economic status of the study population

Table 2. Family history of epilepsy of the study group

Family H/O epilepsy	Study group			P value
	Epileptic n (%)	Control n(%)	Total	
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

Table 3. Character of seizure of the study population

Character of seizure	Study group			P value
	Epileptic n (%)	Control n (%)	Total	
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

Table 4. EEG findings of the study population

EEG findings	Study group			P value
	Epileptic n(%)	Control n(%)	Total	
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

Table 5. Mean difference of serum copper level of the epileptic group and control group

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

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

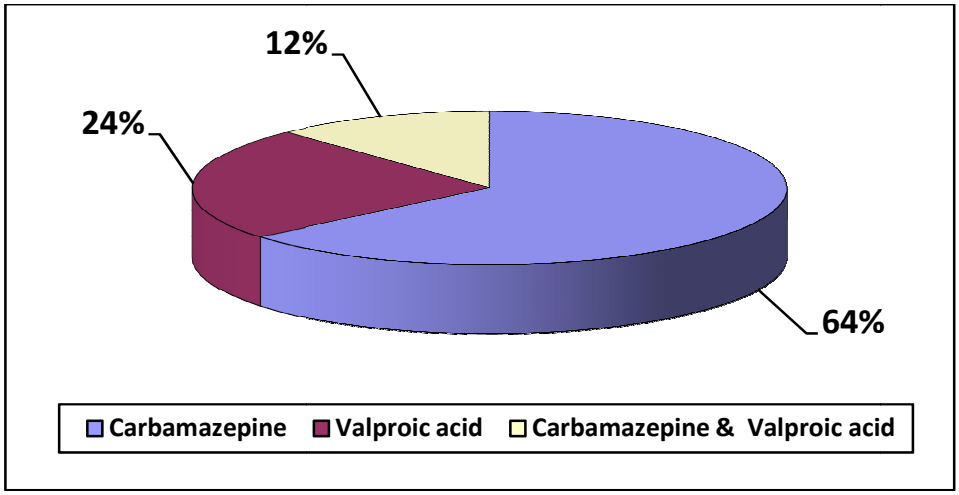

Fig. 2. Type of usage of anti-epileptic drug

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 6. Mean Cu (µg/ml) level between different anti epileptic drugs

	Epileptic patients			P value
	Carbamazepine	Valproic acid	Carbamazepine and valproic acid	
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

The Table 2 shows 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).

The Table 3 shows that the 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).

EEG findings show that generalized seizure in epileptic group was 64% which in control group was 54%. Focal seizure in epileptic group was 36% and in control group 46%, which were not statistically significant (p>0.05).

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.

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).

4. DISCUSSION

Childhood epilepsy is a worldwide problem.It 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 years. In epileptic group mean age was 4.08±2.21 years and control group was 4.70±2.45 years. Approximately similar result was found in the study by Tekinet al. [15] where mean age was 4.24±0.35 years and 4.69±1.12 years among case and control group respectively. Another study by Saboktakin et al. [17] also corroborates with our study. Diop et al's study in Senegal [22] 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 as 1.63:1. A study by Nouri et al. [18] demonstrated that male-to-female ratio as 1.75:1, which corroborate with our study.

In this study, epileptic group had 34% family history of epilepsy, while in control group it was 16% 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 [17].

This study indicates that 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 were not statistically significant (p>0.05). Ogunlesi T et al. [23] reported that generalized tonic-clonic seizures were the commonest seizure type of their study (76.9%). These were followed by tonic seizures (6.3%), clonic seizures (4.8%) and myoclonus (2.4%) that match with this present study.

Following the clinical diagnosis of epilepsy in an individual Osuntokon BO et al. [24] demonstrated that it was usually recommended an EEG, amongst other investigations, be carried out. 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 [25] conducted one EEG-based study 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. 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 [26,27].

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, which was statistically significant ($p<0.05$). Studies of Saboktakin et al. [17], Barbeaus et al. [28] and Verrotti et al. [29] have also corroborated with the similar results of our study. 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. [29] 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 ($p<0.05$).

Studies of Sherifa et al. [30] 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.

5. 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.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline consent of parents of the participants and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle3.com/review-history/48415