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## ASSESSMENT OF SERUM ZINC LEVEL IN CHILDHOOD EPILEPSY TREATED WITH LONG-TERM ANTI EPILEPTIC DRUG (AED)

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### ABSTRACT

Almost 85% of epilepsy patients which is a common neurological disease live in developing world. Mostly the disease start in childhood in more than half of the cases. Long term use of antiepileptic drugs may alter serum zinc level. The purpose of the present study was to assess the serum zinc level in childhood epilepsy treated with long-term Anti-Epileptic Drug (AED). This cross-sectional study was carried out in the outdoor and indoor patient department of Pediatric neurology, BSMMU during the period from March 2013 to August 2013. Sample size was one hundred, among these fifty were case e.g. epileptic child who had received anti-epileptic drugs (Carbamazepine and/or Valproic acid) for more than three months and fifty were control e.g. newly diagnosed epileptic child, who have not yet received antiepileptic drugs. In this study, among 100 epileptic child, mean serum zinc level in case group was  $0.36(\pm 0.20)$  ( $\mu\text{g/ml}$ ) and in control group was  $0.52(\pm 0.26)$  ( $\mu\text{g/ml}$ ), which was statistically significant ( $p < 0.05$ ). The use of one drug or multiple drugs in the treatment of epileptic patients has made the significant low serum zinc level.

**Keywords:** Serum Zinc, 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 result of this discharge is that patient suffer convulsive movements, disturbance of sensation, and loss of consciousness or combination.<sup>1</sup> Epilepsy is a common neurological disease and its occurrence is about 3 to 20 people per 1000 in general population occurring more frequently in school children.<sup>1,2,3,4</sup> In It is estimated that there are 1.52 million patients of epilepsy in Bangladesh. A survey related to the Dasher Kandi, Bangladesh shows that there is about 2.54 patient in every 1000 population in Bangladesh.<sup>5</sup> it is estimated that two third of epileptic seizures starts in age of less than 5 years and seizures assumes the most array of form. Trace elements (e.g. Copper, Zinc and Manganese) are minor building components in tissues including the nervous system. For maintaining human health, there is required balance in trace elements<sup>7</sup>. In peripheral and central nervous systems, trace elements function is vital<sup>8-13</sup>. Indispensable components for certain enzymes (such as glutathione peroxidases) include zinc, Selenium and Copper which are responsible for brain metabolic processes<sup>14 15</sup>.

If there is excess or deficiency of trace elements in some patient so it can lead to some disease<sup>16</sup>. The function of anti-epileptic drug is to change the blood trace elements like Zinc and metabolism. . Sözüer et al<sup>20</sup> measured serum Zinc (Zn) levels in 52 epileptic children who were treated with either Carbamazepine (CBZ) or Valproic acid (VPA) or with a combination of CBZ and VPA. Serum Zn levels were significantly lower in the epileptics than in the two control groups which consisted of 7 untreated epileptics and 12 normal children.

## 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 hundred, among these fifty were case e.g. epileptic child who had received anti-epileptic drugs (Carbamazepine and/or Valproic acid) for more than three months and fifty were 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  $\geq$  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 cases, complete history had taken from accompanying attendants. Through clinical examination was done. Relevant investigation reports were collected and recorded. Serum zinc (Zn) were measured by atomic absorption spectrophotometer<sup>17</sup>. The name of spectrophotometer is graphite furnace 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.

## 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( $\pm$ 2.34) years whereas case group was 4.08( $\pm$ 2.21) years and control group was 4.70( $\pm$ 2.45) years.

**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
>2 to 5 years	21(42)	16(32)	37
>5 years	13(26)	20(40)	33
Total	50(100)	50(100)	100
Mean $\pm$ SD	4.08( $\pm$ 2.21)	4.70( $\pm$ 2.45)	4.39( $\pm$ 2.34)

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

**Table 2: Sex distribution of the study group**

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

**Table 3: Family history of epilepsy of the study group**

Family H/O Epilepsy	Study group		Total	P value
	Epileptic n(%)	Control n(%)		
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			P value
	Epileptic n(%)	Control n(%)	Total	
Generalized tonic clonic	39(78)	36(72)	75	<b>0.57</b>
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 5: EEG findings of the study population**

EEG findings	Study group			P value
	Epileptic n(%)	Control n(%)	Total	
Generalized seizures	32(64)	27(54)	59	<b>0.30</b>
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 zinc level of the epileptic group and control group.**

	Study group			P value
	Epileptic	Control		
Zn ( $\mu\text{g/ml}$ )	0.36( $\pm 0.20$ )	0.52( $\pm 0.26$ )		<0.001

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

Mean zinc level 0.36( $\pm 0.20$ )( $\mu\text{g/ml}$ ) was in epileptic group and 0.52( $\pm 0.26$ ) was in control group where ( $p < 0.05$ ) that was statistically significant.

**Table 7: Mean Zn ( $\mu\text{g/ml}$ ) level between different anti-epileptic drugs**

	Epileptic patients			P value
	Carbamazepine	Valproic acid	Carbamazepine and Valproic acid	
Zn ( $\mu\text{g/ml}$ )	0.38( $\pm 0.25$ )	0.41( $\pm 0.23$ )	0.31 ( $\pm 0.13$ )	0.03

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 zinc levels were  $0.38(\pm 0.25)$  ( $\mu\text{g/ml}$ ),  $0.41(\pm 0.23)$  ( $\mu\text{g/ml}$ ) and  $0.31 (\pm 0.13)$  ( $\mu\text{g/ml}$ ) respectively where ( $p < 0.05$ ) that was statistically significant.

## 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 zinc (Zn) 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  $4.39(\pm 2.34)$ . In epileptic group mean age was  $4.08(\pm 2.21)$  and control group was  $4.70(\pm 2.45)$ . As compared with Tekinet al.<sup>21</sup> study mean age group was  $4.24(\pm 0.35)$  and case group was  $4.69(\pm 1.12)$  that result was approximately similar to our study. Another study by Saboktakin et al<sup>24</sup> also corroborates with our study. Diop et al's<sup>25</sup> study in Senegal 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.<sup>26</sup>

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.<sup>24</sup>

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%)<sup>27</sup> 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.<sup>28,29</sup> 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.<sup>30</sup> It is crucial to recognize that a normal EEG does not exclude epilepsy, as around 10% of patients with epilepsy never show epileptic form discharges. Secondly, an abnormal EEG demonstrating IED (interictalepileptiform 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.<sup>31,32.</sup>

In this present study mean zinc level was  $0.36(\pm 0.20)$  ( $\mu\text{g/ml}$ ) in epileptic group and  $0.52(\pm 0.26)$  ( $\mu\text{g/ml}$ ) in control group which was statistically significant ( $p < 0.05$ ). Studies of Saboktakin et.al.<sup>24</sup>, Barbeauset.al.<sup>23</sup> and Verrotti et.al.<sup>22</sup> have also corroborated with the similar results of our study on serum zinc in epileptic patient under drug therapy. Saboktakin et al demonstrated that the mean zinc level in children with epilepsy under drug treatment was  $0.36(\pm 0.13)$   $\mu\text{g/ml}$  and  $0.43 (\pm 0.21)$   $\mu\text{g/ml}$  in control group, which was lower meaningfully in epileptic patients. Although their control group were normal healthy subjects. Besides this, Verrotti's et al.<sup>22</sup> 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 zinc levels were  $0.38(\pm 0.25)$  ( $\mu\text{g/ml}$ ),  $0.41(\pm 0.23)$  ( $\mu\text{g/ml}$ ) and  $0.31 (\pm 0.13)$  ( $\mu\text{g/ml}$ ) respectively where ( $p < 0.05$ ) that was statistically significant. Here we observed that combination therapy(CBZ+VPA) has more potentiality than monotherapy with CBZ or VPA for reducing serum zinc level of epileptic patients.

Studies of Sherifa et.al.<sup>33</sup>, Sözüer DT<sup>20</sup> et al have also corroborated with the similar results with our study on serum zinc in epileptic patients. Sherifa and colleagues demonstrated that serum level of zinc in patients with epilepsy on treatment (particularly with sodium valproate and carbamazepine) were low.<sup>33</sup>

In Sözüer DT et al<sup>20</sup> demonstrated that zinc level was  $0.27 \pm 0.10$  ( $\mu\text{g/ml}$ ) in patients treated with carbamazepine and  $0.35 \pm 0.15$  ( $\mu\text{g/ml}$ ) in patients treated with sodium valproate. That result was showed carbamazepine was more effective than sodium valproate reducing serum zinc level of epileptic patients.

Yanagisawa et al reported that serum zinc level 31-59  $\mu\text{g/dl}$  ( $0.31-0.59$   $\mu\text{g/ml}$ ) may or may not produce any symptom of zinc deficiency. They stated this reference range as deficiency state and suggested countermeasures this condition either by cause identification and removed as needed or dietary therapy (ingestion of zinc rich food) or zinc replacement. They mentioned that serum zinc level below 30  $\mu\text{g/dl}$  ( $0.30$   $\mu\text{g/ml}$ ) as a definite deficiency state and produce clinical symptom like hair loss, diarrhea, delayed sexual maturation, impotence, hypogonadism, growth retardation, eye and skin lesions, weight loss, delayed healing of wounds, fever, pica, taste abnormalities, mental lethargy, intention tremor, depression, impaired concentration, nystagmus,

dysarthria, night blindness, hypogeusia, anosmia, dementia etc. They recommended dietary allowance for zinc taken by mouth is: 2 milligrams oral zinc for 0 to six months of age; 3 milligrams for seven months to three years of age; 5 milligrams for 4-8 year-olds; 8 milligrams for 9-13 year-olds; 11 milligrams for 14-18 year old boy; 9 milligrams for 14-18 year-old girl.<sup>34-35.</sup>

As antiepileptic therapy (CBZ,VPA,CBZ and VPA) has significant potentiality to reduce serum zinc level in epileptic patients that may lead to morbidity due to zinc derangement therefore, repeated monitoring should be carried out.

### CONCLUSION

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

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