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Original Research Article

Association of serum magnesium levels with seizure disorder; experience from central India

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ABSTRACT

Introduction: Magnesium is the fourth most abundant cation in the body. It has several functions in the human body including its role as a cofactor for more than 300 enzymatic reactions. Mg is a potential modulator of seizure activity because of its ability to antagonize the excitatory calcium influx through the N-methyl-D-aspartate receptor. Low magnesium levels in people with refractory epilepsy can increase the frequency of seizures. Hence in our study we aim to study the association of serum magnesium levels with seizure disorders and compare it with matched controls.

Materials and Methods: In our study 154 adult individuals were included with seizure patients to control ratio of 1:1. Serum Magnesium levels was estimated in all individuals and levels were compared between patients of seizure disorder and healthy controls.

Results: Mean serum magnesium level was significantly lower in patients of seizure disorder as compared to controls ($p<0.01$). We, also observed significantly lower calcium level amongst cases as compared to controls ($p<0.05$). The mean magnesium level within 24 hours of seizures was 1.47±0.50 mg/dl whereas as the duration since seizures increased, mean magnesium level increased.

Conclusion: In our study we found significant association between seizures and serum magnesium levels, as low magnesium has been implicated in refractory seizures which are resistant to anti-epileptic drugs and magnesium supplementation in such patients may result in decrease in number of anti-epileptic drugs and better control of seizures.

1. Introduction

Neuronal excitability is controlled by the balance between excitatory an inhibitory effect, both intrinsic and synaptic. Epileptic events consist of huge excitatory post synaptic potentials which are expression of synchronous burst firing of many neurons.

Magnesium (Mg) is the fourth most abundant cation in the body.[1] It has several functions in the human body including its role as a cofactor for more than 300 enzymatic reactions. Several studies have shown that hypomagnesaemia is a common electrolyte derangement in clinical setting especially in patients admitted to intensive care unit where it has been found to be associated with increased mortality and hospital stay.

Mg is a potential modulator of seizure activity (because of its ability to antagonize the excitatory calcium influx through the N-methyl-D-aspartate (NMDA) receptor), its reduced serum levels in people with refractory epilepsy can increase the frequency of seizures in these individuals.[2]

Hypomagnesemia results in a state of neuronal hyper excitability convulsions and various psychiatric symptoms. AMPA and Kainite receptors intervene mediate fast excitatory transmission. NMDA receptors mediate delayed phase of excitatory neurotransmission. Opening of AMPA/ Kinase receptors depolarizes the neuronal cell membrane,

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releasing the magnesium block of the NMDA receptor. With the removal of magnesium block, NMDA receptors, which are colocalized with AMPA receptor, become activated.

Thus, the aim of our study is to find the association of serum magnesium levels with seizure disorders and whether magnesium deficiency plays a primary role in the development of seizure activity.

2. Materials and Methods

Seventy-seven subject who had a convulsive episode in past 72 hours who presented to the emergency department of Peoples College of medical sciences and research Centre were included in the study along with age and sex matched healthy individuals who attended the general OPD.

2.1. Inclusion criteria

1. Patients diagnosed as having seizures on clinical basis admitted in our hospital aged 15 to 70 years.
2. Who were willing to participate in the study by giving consent themselves or through their guardian.

2.2. Exclusion criteria

1. Patients who denied consent
2. Patients presenting after 72 hours of seizure episode
3. Those on magnesium supplements
4. Pregnant females with Pre-eclampsia/ Eclampsia.

The laboratory parameters that were assessed along with magnesium were Serum Calcium, Serum Sodium, and Blood Glucose (at the time of seizure/admission) by capillary prick.

CT/MRI and EEG was not done for all patients due to financial limitations.

The laboratory parameters were also estimated in general population taken as controls.

Reference range of parameters estimated:

1. Serum Magnesium: 1.8 to 2.2 mg/dl
2. Serum Calcium: 9 to 11 mg/dl
3. Sodium: 136 to 145 meq/L
4. Blood Glucose: <70 mg/dl

3. Results

The study enrolled 77 patients with seizures and 77 matched controls fulfilling the inclusion criteria during the study period. The baseline characteristics of patients are described in able 1Table 1.

The mean age of cases in present study was 44.74±16.73 years whereas mean age of patients in control group was 45.44±15.52 years. Test of significance observed no statistical difference in age composition between cases and control (p>0.05).

Maximum patients in both the groups were male and were 59.7% amongst cases and 74% amongst controls. Cases and controls were comparable in sex composition (p>0.05).

In our study the mean magnesium level in cases was 1.60±0.49 mg/dl whereas that in control was 2.05±0.32 mg/dl. Test of significance (unpaired t test) observed significantly lower magnesium level amongst cases as compared to control (p<0.01) described inTable 1. Distribution of calcium, sodium, random blood sugar levels are described in Table 1.

In our study out of 77 patients with seizures 61 had Mg levels <1.8 mg/dl, 12 had Mg levels between 1.8-2.2 mg/dl and 4 patients had Mg level >2.2 mg/dl and 39 had hypocalcemia (<8.5 mg/dl) whereas 38 had normal serum calcium levels (8.5-11 mg/dl).

In present study, mean magnesium level within 24 hours of seizures was 1.47±0.50 mg/dl whereas as the duration since seizures increased, mean magnesium level increased. Test of significance (ANOVA) observed statistically highly significant difference in mean magnesium level and time since seizures (p<0.01) as described in Table 2.

In present study, most common cause for seizures was organic in 64.9% patients followed by metabolic and isolated unspecified in 24.7% and 10.4% patients respectively as described in Figure 1.

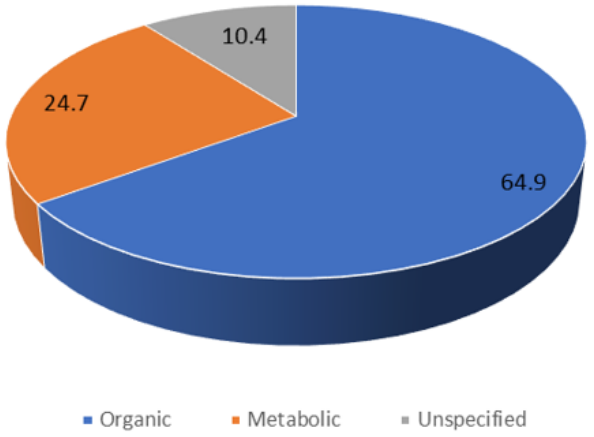

Fig. 1: Distribution according to cause of seizures amongst cases

4. Discussion

In the present study we tried to determine whether there is any association of magnesium with seizure disorders, though magnesium is implicated in seizures due to eclampsia it is hypothesized that it may play a pivotal role in other forms of seizures as well.

The study was case control study where the variables were compared with age and sex matched controls.

Table 1: Baselinecharacteristics of our patients

	Cases (n=77)	Controls (n=77)	P Value
1) Age	44.74±16.73	45.44±15.52	0.29
2) Gender			
Male	59.7%	74%	0.06
Female	40.3%	26%	
3) Sr. Magnesium (mg/dl)	1.60±0.49	2.05±0.32	**0.001**
4) Sr. Calcium (mg/dl)	8.99±0.75	9.32±1.11	**0.03**
5) Sr. Sodium (meq/l)	138.3±5.8	138.4±3.6	0.93
6) Blood Glucose (mg/dl)	129.64±47.35	128.84±31.79	0.90

Table 2: Association of time since seizure with magnesium level amongst cases

Magnesium (mg/dl)	Time since seizure (Hours)		
	<24	24-48	>48
Mean	1.47	1.80	1.88
SD	0.50	0.41	0.35
P value		0.0008	

The cause of seizures varies with age. Mean age of cases in present study was 44.74±16.73 years whereas mean age of patients in control group was 45.44±15.52 years. Majority of patients in both the groups were male i.e. 59.7% amongst cases and 74% amongst controls. Cases and controls were comparable in age and sex composition (p>0.05).

Mean magnesium level in cases (1.60±0.49 mg/dl) was significantly lower than that in control (2.05±0.32 mg/dl) in present study and was statistically significant (p<0.01). These findings were supported by C Ramakrishna et al[3] in which mean magnesium level was significantly lower in cases (0.96±0.58) with seizures as compared to controls (2.04±0.28) without seizures (p<0.01). Our findings also correlate with the study of Oladipo O et al,[4] in which mean plasma Magnesium in the patients was significantly lower than that obtained in the controls (P<0.001). Bharathi S et al[5] established statistically significant association between hypomagnesemia and "Typical Febrile convulsions" in their study on pediatric group of population. Thus, suggesting the role of hypomagnesemia even in cases of febrile convulsions. Thus, there is some association of magnesium and seizures either causal or as an after effect of seizures.

The present study observed significantly (unpaired t test) lower calcium level amongst cases i.e., 8.99±0.75 mg/dl as compared to controls i.e., 9.32±1.11 mg/dl (p<0.05). Deficiency of magnesium is often seen to be associated with hypocalcemia as the production of cyclic adenosine monophosphate (cAMP) is magnesium dependent, which in turn controls the release of parathyroid hormone and thus magnesium effects calcium metabolism. These findings are in concordance with the findings of Abdullahi I et al[6] where mean serum calcium in the 60 cases was significantly lower than the control cases (2.3 ± 0.13 mmol/L vs. 2.4 ± 0.12 mmol/L; P < 0.001).

Mean sodium amongst cases was 138.3±5.8 meq/L and that amongst controls was 138.4±3.6 meq/L whereas mean potassium level was 4.16±0.59 and 4.27±0.62 meq/ L in cases and controls respectively, however no significant difference in mean sodium and potassium levels was observed between cases and controls in present study.

Our study included 4 hypoglycemics with seizures and 2 patients with RBS high enough to cause seizures (244 mg/dl and 362 mg/dl respectively) but this may not be the sole cause of seizures in them, since one was having alcohol intoxication and the other had acute ischemic stroke. However, no statistical difference was observed in mean RBS between cases and controls (p>0.05).

In present study, mean magnesium level in cases with first seizure was lower (1.58±0.50 mg/dl) as Compared to other cases (1.65±0.49 mg/dl) but the observed difference was statistically insignificant (p>0.05). It was observed in present study that mean magnesium level was significantly less amongst cases within 24 hours of seizures (1.47±0.50 mg/dl) and as the duration since seizure onset increased, mean magnesium level increased as evidenced by previous studies in which Magnesium levels decreased in patients with seizure disorders and the mean values were lower when time elapsed since onset of seizure is shorter thus confirming the possible role of magnesium in the pathophysiology of seizures.[3] Similar findings were reported by Horacio M et al[7] where magnesium level was lower when time elapsed after convulsion was shorter. Thus, following acute attack of seizure, serum magnesium tends to normalize with the time.

Cases were distributed on the basis of probable cause of seizure. The most common cause for seizures was organic in 64.9% patients followed by metabolic in 24.7% and unspecified in 10.4% cases. Organic causes included CVA (n=23), meningitis bacterial/viral/tubercular or encephalitis (n=22), cortical venous thrombosis (n=1), drug withdrawal (n=3), and RTA (n=2) whereas metabolic causes were

related to hypoglycemia (n=4), electrolyte imbalances (n=9) and alcohol related (n=5).

The present study observed no statistical difference in mean magnesium level in various causes of seizures (p>0.05) and due to lack of imaging modalities and further investigations.

Magnesium as a cause for seizure could not be determined and might need further evaluation, however some cases with unspecified seizures (n=8) did indeed have hypomagnesemia (n=6) as the only serum abnormality with normal metabolic parameters, who also had intractable seizures instead of triple drug therapy, but still due to financial constraints extensive investigations could not be carried out to confirm isolated hypomagnesemia as cause of seizures in these patients. These patients responded well to magnesium therapy in the form of intravenous magnesium sulphate 1gm iv tid, indicating that magnesium does in fact play a role in seizure pathogenesis as shown in study by Abdelmalik PA et al.[8]

However 1 patient out of the 6 unspecified had normal MRI and EEG and responded well to magnesium supplements.

5. Conclusion

It remains a matter of debate whether magnesium deficiency plays a primary role in the development of seizure activity. In our study we found that the mean magnesium level difference in cases and controls was statistically significant implicating some association between seizures and serum magnesium levels. Magnesium levels correspond with the time since seizure with mean magnesium levels being lowest immediately after seizure activity and increasing as the time elapse after the seizure, thus confirming the possible role of magnesium in the pathophysiology of seizures.

Isolated hypomagnesemia was found in 6 cases with no other apparent cause of seizure, who had refractory seizures and responded well to magnesium supplements, though these cases did need further evaluation like MRI and EEG but still possibility of hypomagnesemia as a cause could not be ruled out.

Although magnesium as a cause for seizure could not be easily determined due to limitations but still magnesium has been implicated in refractory seizures which are resistant to anti- epileptic drug and magnesium supplementation in form of IV Magnesium sulfate or oral Magnesium oxide in such patients resulted in decreased number of anti- epileptic drug and better control of seizures.

6. Limitations

1. Small sample size and all Patients taken from a single Centre.
2. Radiological investigations (MRI/CT and EEG not done for all patient due financial constraints.

7. Conflict of Interest

There are no conflicts of interest in this article.

8. Source of Funding

None.

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