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Original Article

Biochemistry Section

Serum Magnesium Levels and Lipid Profile in Patients with Epileptic Seizures: A Cross-sectional Study

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ABSTRACT

Introduction: Recurrent seizures of cerebral origin with episodes of sensory, motor, or autonomic expression, with or without loss of consciousness, are typical symptoms of epilepsy, a chronic neurological condition. As a voltage-dependent calcium channel antagonist, magnesium inhibits calcium ion release, which reduces neuronal excitability in hypomagnesemia. It is well recognised that the most frequently prescribed Anti-epileptic Drugs (AEDs), namely carbamazepine, phenytoin, and phenobarbital, have adverse effects on lipid profiles.

Aim: To compare the levels of serum magnesium and serum lipid profiles in patients with epileptic seizures and healthy controls.

Materials and Methods: The present cross-sectional study included 50 clinically diagnosed patients with epileptic seizures, aged between 18-60 years, and 50 age and sex-matched healthy controls visiting the Department of Neurology, Mahatma Gandhi Medical College (MGMC), Jaipur, Rajasthan, India from October 2019 to March 2020. A 5 mL venous blood sample was collected for biochemical investigations such as serum magnesium, serum Total Cholesterol (TC), serum Triglycerides (TG), serum High Density Lipoprotein cholesterol (HDL-C), serum Low Density Lipoprotein cholesterol (LDL-C), and serum Very Low Density Lipoprotein cholesterol (VLDL-C) and assayed. Student's t-test was applied, and a p-value of <0.05 was considered statistically significant.

Results: In the present study, epileptic cases (n=50) included 35 male patients and 15 female patients with a mean age of 36.1±15.56 years, and healthy controls (n=50) included 37 male patients and 13 female patients with a mean age of 38.26±8.54 years. When compared to healthy controls, patients with epileptic seizures had lower serum magnesium levels with mean values of 4.18±1.22 and 2.12±1.00, respectively (p-value ≤0.001). Patients with epileptic seizures had higher values of the serum lipid profile, i.e., serum TG, TC, low-density lipoprotein cholesterol, and very low-density lipoprotein cholesterol than healthy controls with a p-value ≤0.001, which is statistically significant. On the contrary, serum HDL-C levels in epileptic patients (43.68±7.37 mg/dL) are lower than healthy controls (49.69±5.73 mg/dL).

Conclusion: Correcting the serum magnesium levels in people with epileptic seizures may help reduce the intensity of the seizures.

Keywords: Cholesterol, Epilepsy, Excitotoxicity, Glutamate, Hypomagnesemia

INTRODUCTION

A chronic neurological disorder called epilepsy is characterised by recurrent seizures, varying in frequency from once a year to multiple times daily [1]. Patients who take AEDs like carbamazepine and phenytoin over an extended period have shown disorders such as Myocardial Infarction (MI), stroke, and atherosclerosis [2]. Magnesium, a significant macro-mineral, acts as a co-factor in numerous enzyme activities [3]. It is crucial for optimal nerve transmission, neuromuscular coordination, and protection against excitotoxicity [4]. As magnesium can act as a chemical gatekeeper, its deficiency increases calcium entry into nerve cells, leading to overstimulation, convulsions, and spasms [5]. Long-term antiepileptic therapy is associated with various metabolic abnormalities in tissue and organ systems, including the liver [6]. The health of the liver and the activity of the hepatic microsomal enzyme system may be affected by anticonvulsants [6].

Anti-epileptic Drugs (AEDs) induce hyperlipidemia by stimulating the p450 enzyme system in the liver [7]. In patients with epilepsy, the risk of cardiovascular death is 1.5-2.5 times higher than in the general population [8]. Therefore, evaluating changes in serum lipid levels following antiepileptic drugs may assist in selecting the safest drug and preventing cardiovascular complications later in life. Similar research was conducted by Yuen AW and Sander JW, suggesting that magnesium may play a role in epilepsy, and thus recognising and correlating hypomagnesemia may aid in seizures control and clinical outcomes [9].

Based on the literature review and authors limited knowledge, most studies like those by Aggarwal J et al., and Divya P et al., have focused on young children taking AEDs. The lack of sufficient data from the adult population of epilepsy treated with multiple AEDs for atleast six months prompted us to assess and compare lipid parameter levels, as well as serum magnesium concentrations, among epileptic patients and healthy controls [10,11].

Therefore, the current study was designed to evaluate the impact of serum magnesium levels and lipid profiles (TG, TC, HDL-C, LDL-C, and VLDL-C) in present epileptic patients and to compare these parameters with those of healthy controls.

MATERIALS AND METHODS

The cross-sectional study was conducted in the Department of Biochemistry in association with the Department of Neurology at Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India over a six-month period from October 2019 to March 2020. The study was carried out after obtaining approval from the Institutional Ethics Committee (IEC) (vide letter number MGMCH/JPR/06.26/09/2019). Written informed consent was obtained from all participants after explaining the research purpose.

Inclusion criteria: Patients diagnosed with epileptic seizures (as per guidelines by the International League Against Epilepsy (ILAE) [12]) and regularly taking AEDs for the last six months or more within the age group of 18-60 years were included. The control group consisted of 50 age- and sex-matched healthy subjects. An

equivalent number of adults who attended the general Outpatient Department of Ophthalmology and were otherwise health were included as controls.

Exclusion criteria: Patients with thyroid dysfunction, cardiovascular disease, chronic liver disease, cancer, pregnant or lactating women, and individuals aged ≤18 years were excluded from the study.

Sample size calculation: The sample size was calculated by Cochran's formula:

$$n=\frac{z^2(pq)}{e^2}$$

Where, n=sample size

z=confidence level at 95% (1.96)

p=prevalence (1%) [13]

q=(100-p)

e=maximum allowance of error (5%)

So, putting the values into the formula:

n=(1.96) 2 *1*99/(5)2

=3.84*1*99/25

=380.16/25

Therefore, the final calculated sample size in the present study was 15.20.

Study Procedure

Total 5 mL venous blood samples were collected using standard aseptic protocols. The collected samples were analysed on the fully auto-analyser VITROS 5600 and were subjected to investigations for serum magnesium, Total Cholesterol (TC), HDL Cholesterol (HDL-C), LDL Cholesterol (LDL-C), VLDL Cholesterol (VLDL-C), and Triglycerides (TG). Serum magnesium was assessed using the Formazan dye method, TC was assessed using the cholesterol oxidase peroxidase enzyme method, HDL-C was assessed using the direct method, and serum TG was assessed using the glycerol peroxidase method, endpoint as shown in [Table/Fig-1] [14-18].

Parameters	Method	Cut-off value
Serum magnesium	Formazan dye method [14]	1.6-2.3 mg/dL
Serum Total Cholesterol (TC)	CHOD-PAP method [15]	<200 mg/dL
Serum HDL-cholesterol	Direct method [16]	>60 mg/dL
Serum LDL-cholesterol	Calculated parameter [17]	100-129 mg/dL
Serum VLDL-cholesterol	Calculated parameter [17]	TG/5
Serum Triglycerides (TG)	Enzymatic, End Point [18]	<150 mg/dL

[Table/Fig-1]: Different parameters, methods for estimation and their cut-off range [14-18].
CHOD-PAP: Cholesterol oxidase P-aminophenazone

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences (SPSS) Version 21.0 was used to analyse the data. Means and standard deviations were used to summarise continuous variables. The patients' outcomes were compared to those of the control group using Student's Independent t-test. A probability of less than 5% was considered statistically significant for all parameters (p=value ≤0.05).

RESULTS

In the present study, the epileptic cases (n=50) included 35 male patients and 15 female patients with a mean age of 36.1±15.56 years, while the healthy controls (n=50) included 37 male patients and 13 female patients with a mean age of 38.26±8.54 years. Upon applying a Student's t-test between the two groups, the obtained t-value for age was 0.860, which was found to be statistically non significant with a p-value of 0.391. Equal distribution in gender was ensured to maintain compatibility between both groups, and its p-value was 0.259, also found to be statistically non significant [Table/Fig-2].

Parameters	Controls (n=50)	Epileptic seizure (n=50)	t-value	p-value
Age (years)	38.26±8.54	36.1±15.56	0.860	0.391
Gender	37- Male 13- Female	35- Male 15- Female	----	0.259
Magnesium (mg/dL)	4.18±1.22	2.12±1.00	9.24	<0.001*
TC (mg/dL)	114.48±42.67	221.41±33.95	-13.86	<0.001*
TG (mg/dL)	102.08±21.07	168.99±22.84	-15.22	<0.001*
HDL-C (mg/dL)	49.69±5.73	43.68±7.37	4.55	<0.001*
LDL-C (mg/dL)	126.09±22.97	143.65±31.20	-3.2	<0.001*
VLDL-C (mg/dL)	17.57±7.27	33.97±4.78	-13.32	<0.001*

[Table/Fig-2]: Comparison of serum magnesium levels and serum lipid profile between epileptic seizure and control group.
HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL=Very low density lipoprotein; TG: Triglycerides; TC: Total cholesterol; Student t-test applied;
*p-value <0.05=statistically significant

Serum magnesium levels and serum HDL cholesterol levels were significantly lower among the epileptic group compared to healthy controls (p-value ≤0.001) [Table/Fig-2]. The mean serum total cholesterol levels and mean serum triglyceride levels of epileptic seizures patients showed a statistically significant increase compared to healthy controls (p-value ≤0.001), while LDL cholesterol and VLDL cholesterol levels were significantly increased in epileptic cases.

It was observed that most adults were using phenytoin monotherapy [19], followed by phenobarbitone [18] and carbamazepine [13]. Both male and female distributions in the various groups of AEDs were compared in the study. The duration of epileptic seizures was 24.7±12.5 years in males compared to females with 19.5±14.1 years. The treatment of epilepsy lasted for 16.7±7.42 years in males, while the duration of medication in females lasted for 17.8±8.89 years [Table/Fig-3].

Descriptions	Male (n=35)	Female (n=15)	Total (N=50)
Phenytoin (n)	13	6	19
Phenobarbitone (n)	14	4	18
Carbamazepine (n)	8	5	13
Duration of epileptic seizures (years)	24.7±12.5	19.5±14.1	23.12±13.07
Duration of medication (years)	16.7±7.42	17.8±8.89	17.03±7.81

[Table/Fig-3]: Clinical characteristics of the analysed group of epileptic seizure patients.

Mean serum magnesium levels in male and female epileptic patients taking AEDs has been depicted in [Table/Fig-4]. In males, serum magnesium levels were elevated in carbamazepine (mean 2.13±0.08 mg/dL), followed by those on phenobarbitone and phenytoin. In female epileptic patients, serum magnesium levels were elevated in phenobarbitone (mean 3.05±1.88 mg/dL), followed by phenytoin, with the least levels found in those on carbamazepine (1.97±0.69 mg/dL).

Anti-epileptic Drugs (AEDs)	Serum magnesium levels (mg/dL) (Mean±SD)	
	Male (2.06±0.95)	Female (2.27±1.14)
Phenytoin (n=19)	2.01±1.11	2.00±0.68
Phenobarbitone (n=18)	2.06±0.93	3.05±1.88
Carbamazepine (n=13)	2.13±0.08	1.97±0.69

[Table/Fig-4]: Mean serum magnesium levels in epileptic patients on AEDs compared against that in the specific AEDs group.

DISCUSSION

Patients with epilepsy have to undergo chronic treatment with AEDs. It is important not only that their seizures be under control, but also that adverse effects due to long-term AED use should be minimal. According to the current study, the epileptic cases (n=50) included 35 male patients and 15 female patients with a mean age of 36.1±15.56 years, while the healthy controls (n=50) included 37 male patients and 13 female patients with a mean age of 38.26±8.54 years were enrolled.

The present study shows low serum magnesium levels in epileptic patients compared to healthy subjects. This observation was similar to the study conducted by Osborn KE et al., who reported that serum magnesium levels are lower in epileptic seizures patients compared to healthy controls [19]. A similar study conducted by Krishna CR et al., included 50 cases, and 40 (80%) showed significantly lower magnesium levels, i.e., 0.964±0.58 mg/dL [20]. Theoretically, low magnesium levels could enhance glutamatergic neurotransmission, encourage excitotoxicity, and eventually cause oxidative stress [21]. Since, excessive glutamatergic neurotransmission has been firmly linked to seizures activity, magnesium could potentially reduce the excitotoxicity associated with epilepsy [22].

The serum lipid profile was also evaluated and compared. In contrast to normal controls, epileptic patients receiving AEDs showed elevated levels of blood triglycerides (TG), Total Cholesterol (TC), LDL cholesterol, and VLDL cholesterol. A similar finding by Steinberg D showed that the increase in the level of lipid profile was significantly higher in epileptic patients [23]. He explained that excess levels of serum lipids begin to seep into the inner wall of the artery. This triggers an inflammatory response, which speeds up the accumulation of cholesterol in the artery wall. This, in turn, produces more inflammation. Eventually, the deposited cholesterol hardens into a plaque that can rupture and lead to the blood clots that cause heart attacks and strokes.

Elevated levels of lipid profile concentration, except HDL, during treatment might be associated with an increased risk of vascular disease in patients with epilepsy. A study by Nikolaos T et al., shows similar results, suggesting that long-term use of AEDs raises cholesterol levels [24]. This observation was similar to the study conducted by Manimekalai K et al., who observed statistically significant high mean TC, HDL-C, LDL-C, and TG levels in young adults receiving AEDs compared with the control group [25].

The total duration of epileptic seizures in patients is quite long, while the patients seeking medication started a little later in their life, or there was a delay in treatment. The decision to start AED therapy should be based on an informed analysis of the likelihood of seizures recurrence, the consequences of continuing seizures for patients, and the beneficial and adverse effects of the pharmacological agent chosen [26]. The patients' and family's views should also be considered when AED treatment is begun [27].

Limitation(s)

The parameters could not be studied before the initiation of the AEDs, and therefore, any confounding factors over time could not be eliminated. Secondly, a brief time period was taken for the study.

CONCLUSION(S)

The study showed that, in comparison to healthy patients, epileptic seizures patients had low levels of magnesium and high levels of lipid profile. Due to the long-term administration of AEDs, patients' lipid profiles may become deranged. Therefore, in patients receiving such therapy, physicians should continue to monitor the patient's serum lipid profile. Regular monitoring of these biomarkers can be helpful in selecting an appropriate treatment protocol and overall controlling the mortality and morbidity rate. Screening for neurobehavioral co-morbidities should be an integral part of management with "active" epilepsy.

Author's contribution: MA: Conception and design, acquisition of data; SS: Analysis and interpretation of data; AG: Drafting the article or revising it critically for important intellectual content; SAS: The final approval of the version to be published has been given by the author.

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