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Original Research Article

The relationship between magnesium and seizure control in epileptic patients

Yonathan A. Suparman*, Herlyani Khosama, Corry N. Mahama

Department of Neurology, Faculty of Medicine, Sam Ratulangi University, Manado, Indonesia

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***Correspondence:**
Dr. Yonathan A. Suparman,
E-mail: Yonathan.andrian@gmail.com

ABSTRACT

Background: Magnesium has a central nervous system depressant effect by inhibiting the N-methyl-D-aspartate (NMDA) receptor, an antagonist of calcium channels, and increasing the surface tension of the cell membrane. Patients with epilepsy who had seizures more than 4 times/week had lower serum magnesium levels than those with the episode of less than or equal to 1 time/week. A low dose of magnesium added to phenytoin or carbamazepine can reduce seizure frequency. We want to evaluate the relationship between serum magnesium levels and their dietary intake level with seizure control in Manado.
Methods: Patients with epilepsy aged 18-65 years, from July 2019 to October 2019, were tested for dietary and serum magnesium level in the last 30 days using NutriSurvey software. Regression models were used to quantify the relationship between dietary and serum magnesium level with seizure freedom and its frequency in the last 30 days.
Results: One hundred and ten epileptic patients were included in this study. The median serum magnesium level is 2 mg/dl. There was no significant relationship between serum magnesium levels and seizure freedom (p=0.423) or its frequency in the last 30 days (p=0.966). Dietary magnesium intake (OR 1.01; 95% CI 1.00-1.02, p=0.034) was associated with seizure freedom but not with its frequency (p=0.423).
Conclusions: Dietary magnesium intake was associated with seizure freedom, but serum magnesium levels were not associated with seizure freedom or frequency.

Keywords: Serum magnesium level, Dietary magnesium intake, Seizure freedom, Seizure frequency

INTRODUCTION

According to International league against epilepsy (ILAE), epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and the neurobiological, cognitive, psychological, and social consequences of this condition. It is estimated that about 30% of patients will experience drug resistance and still experience a seizure despite using optimal polytherapy doses.[1–3]

Magnesium is known to have a central nervous system depressant effect. Its mechanism of action includes inhibiting the N-methyl-D-aspartate (NMDA) receptor, as an antagonist of calcium channels and increasing the cell membrane's surface tension, thereby reducing cell excitability.[4]

A study in India found that epileptic patients with seizures>4 times a week had significantly lower serum magnesium levels than those with seizures<1 time/week. Also, magnesium supplementation showed better results in seizure control.[5-7]

Recognizing the critical role of magnesium in epilepsy, the researchers wanted to find out whether serum magnesium levels or its dietary intake that have a relationship with seizure control in Indonesia and particularly in Manado.

METHODS

We used a cross-sectional research design. We conducted this study at the neurology clinic of Professor Dr. R. D. Kandou Hospital, the primary referral center hospital in Manado from July 2019 to October 2019. Patients aged 18-65 years who have had epilepsy for at least one year, were fluent in Indonesian, could follow verbal commands, and had full awareness at the time of the examination were included in this study. They also need to take anti-epileptic drugs regularly in the past year. We excluded patients who had a history of systemic diseases that could affect serum magnesium concentration/absorption in serum such as alcohol poisoning, acute diarrhea, diabetes mellitus, and renal failure, or had a history of taking medications or supplements containing magnesium or affecting serum magnesium levels.

Seizure freedom is defined as free from all forms of seizure, including aura, for at least one year. If patients had been diagnosed with epilepsy in less than a year, seizure freedom is defined as free from all forms of seizure, including aura after a period has elapsed equal to three times the longest preintervention interseizure interval. The frequency of seizures is the number of attacks that occurred in the last 30 days. A blood sample was collected in the neurology clinic to assess the serum magnesium level. Dietary magnesium intake was evaluated using the 24-hour dietary recall method on two regular days and one weekend day (Saturday or Sunday) and calculated using the 2007 survey nutrition software.

We use the statistical software R version 3.6.1 for data analysis. Variable selection in logistic regression and linear regression was carried out stepwise forward using the Bayesian information criteria (BIC) value. Based on the BIC value, variables that had an insignificant relationship in the univariable model could still be included in the multivariable model. Ethical approval was given from ethical committee for medical research of R. D. Kandou Hospital.

Sample size is calculated by using regression logistic.

$$n1 = (Z_{1-\alpha/2} + Z_{1-\beta})^2/P \times (1-P) \times \beta^2$$

We want to have α value of 0.05, then $Z_{1-\alpha/2}$ value is 1.96 and for power (1-P) value of 0.9, then $Z_{1-\beta}$ value is 1.28. The prevalence of drug resistant epilepsy patient is p=0.25 and to anticipate the correlation, we got β value of 0.7 (odd ratio=2). The calculation is as below.

$$n_1 = \frac{(1.96 + 1.28)^2}{[0.25 \times (1-0.25) \times 0.7^2]} = 93$$

In multivariate analysis, if a parsial correlation of R^2 is 0.15, then we need.

$$n = \frac{n_1}{1-R^2} = \frac{93}{1-0.15} = 109.4 = 110\ sample$$

RESULTS

We had a total of 110 epileptic patients with a male to female ratio of about 6:4. Their median age was approximately 33 years (Table 1). Clinical laboratory parameters, including urea, creatinine, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and electrolytes, did not indicate any abnormality in most patients.

The median serum magnesium concentration of the 110 epileptic patients in this study was around 2 mg/dl and interquartile range (IQR) of 1.9-2.2 mg/dl. The median value for women was slightly higher than that of men (2.1 versus 2.0 mg/dl; p=0.014). The amount of magnesium dietary intake level in the last month collected through interviews also showed a significant difference between men and women, with the median of 418 and 309 mg (p<0.001), respectively. The frequency of seizures in the last 30 days has a median value of 1 time in all patients. Meanwhile, the prevalence of controlled seizures among those who came to visit the RSUP during the three months of data collection was 22%.

The relationship between serum magnesium levels in epileptic patients with seizure freedom cannot be proven in this study (Table 2 and 3). After controlling for other variables (multivariable model), serum magnesium increment can be preventive towards controlling epileptic seizures (Table 2).

However, the relationship value interval in the two models includes a zero value. In the context of this linear regression, the direction of the relationship between the two variables can be considered to have happened by chance.

Dietary magnesium intake level shows a relatively small relationship (OR almost one, even though p=0.034). Epileptic patients with a history of status epilepticus had a much greater chance (nearly 5 times, p=0.048) to have seizures freedom after other factors' variability was taken into account.

The univariable model shows that an increment in serum magnesium tends to decrease the frequency of seizure generation (Table 2).

Still, it increases the frequency of seizures slightly after the regression model controls other variables in the data. In this case, dietary magnesium level does not affect in determining the frequency seizure. Patients with more than 25 minutes of sun exposure for at least three days in a week experienced an average of 1.2 less episodes (p=0.001) than those exposed to sunlight less than 25 minutes.

Table 1: Characteristics of one hundred and ten epilepsy patients in the study.

Characteristics	Total (N = 110)		Female (n = 47)		Male (n = 63)		P value
	n (%)	Med (Q1; Q3)	n (%)	Med (Q1; Q3)	n (%)	Med (Q1; Q3)	
Age (years)	*	32.5 (24.0 44.8)	*	33.0 (24.0 43.0)	*	30.0 (23.5 45.0)	0.790
Age at first seizure (years)							
<15	37 (34)	*	19 (40)	*	18 (29)	*	0.272
≥15	73 (66)	*	28 (60)	*	45 (71)	*	
Initial seizure frequency (months)							
0-1	29 (26)	*	10 (21)	*	19 (30)	*	0.408
≥2	81 (74)	*	37 (79)	*	44 (70)	*	
History of status epilepticus	21 (19)	*	8 (17)	*	13 (21)	*	0.817
History of febrile seizure	38 (35)	*	15 (32)	*	23 (37)	*	0.765
Family history of epilepsy	8 (7)	*	4 (9)	*	4 (6)	*	0.722
Sun exposure 3 days per week (min)							
<25	29 (26)	*	15 (32)	*	14 (22)	*	0.356
≥25	81 (74)	*	32 (68)	*	49 (78)	*	
Imaging							
Normal	47 (43)	*	23 (49)	*	24 (38)	*	0.505
Abnormal	46 (42)	*	18 (38)	*	28 (44)	*	
No imaging	17 (15)	*	6 (13)	*	11 (17)	*	
EEG							
Normal	37 (34)	*	14 (30)	*	23 (38)	*	0.512
Abnormal	71 (66)	*	33 (70)	*	38 (62)	*	
Total AED							
1	77 (70)	*	31 (66)	*	46 (57)	*	0.315
2	24 (22)	*	10 (21)	*	14 (22)	*	
3 or more	9 (8)	*	6 (3)	*	3 (5)	*	
Urea (mg/dl)	*	20.0 (15.0 23.0)	*	17.5 (13.0 20.0)	*	20.0 (17.0 26.0)	0.004
Creatinine (mg/dl)	*	0.8 (0.6 0.9)	*	0.7 (0.6 0.8)	*	0.8 (0.7 1.1)	<0.001
SGOT (mg/dl)	*	20.0 (19.0 24.0)	*	20.0 (18.0 23.0)	*	20.0 (20.0 25.0)	0.471
SGPT (mg/dl)	*	17.0 (13.0 27.5)	*	15.0 (12.0 18.0)	*	18.0 (15.0 30.0)	0.022
Sodium (mEq/l)	*	138.0 (136.0 139.0)	*	138.0 (137.0 139.0)	*	138.0(136.0 140.0)	0.993
Potassium (mEq/l)	*	3.8 (3.6 4,2)	*	3.8 (3.6 4,2)	*	3.8 (3.5 4.0)	0.270
Chloride (mEq/l)	*	102.0 (98 105)	*	99.9 (98.0 104.8)	*	102.3(98.0 107.0)	0.579
Dietary magnesium	*	380.5(312.2, 454.7)	*	309.1(293.4 358.6)	*	418.4(379.8 469.6)	<0.001
Magnesium serum (mg/dl)	*	2.0 (1.9 2.2)	*	2.1 (2.0 2.2)	*	2.0 (1.8 2.2)	0.014
Seizure frequency	*	1.0 (0.0 1.0)	*	0.0 (0.0 1.0)	*	1.0 (0.0 1.0)	0.380
Seizure freedom	24 (22)	*	8 (17)	*	16 (25)	*	0.413

Med-median, Q1-quartile I, Q3-quartile III, a-t test or Mann-Whitney U according to the normality of distribution on numerical variables, c2-test on categorical variables, b-in the last 30 days

Table 2: Logistic regression model seizure freedom in epilepsy patients.

Variables	Univariable model		Multivariable model	
	OR (95% CI)	P	OR (95% CI)	P
Magnesium serum	0.80 (0.32-2.00)	0.639	0.70 (0.29-1.68)	0.423
Dietary magnesium	1.00 (1.00-1.01)	0.080	1.01 (1.00-1.02)	0.034
Age	1.01 (0.98-1.04)	0.585	*	
Male versus female	1.66 (0.64-4.29)	0.295	*	
Age at first seizure (years)				
<15 (ref)				
≥15	2.25 (0.77-6.62)	0.140	*	
Initial seizure frequency (months)				
≥2 (ref)				0.004
0-1	0.25 (0.09-0.64)	0.004	10.24 (2.11-49.81)	
History of status epilepticus	1.58 (0.54-4.64)	0.407	5.81 (1.02-33.16)	0.048
History of febrile seizure	0.93 (0.36-2.43)	0.888	*	
Family history	1.21 (0.23-6.43)	0.821	*	
Sun exposure 3 days per week	0.65 (0.24-1.72)	0.383	*	
Imaging				
Normal (ref)				
Abnormal	1.17 (0.43-3.22)	0.757	*	
No imaging	1.76 (0.49-6.27)	0.384	*	
EEG				
Abnormal versus normal	0.95 (0.36-2.48)	0.914	*	
Total AED				
1 OAE (ref)				
2 OAEs	1.18 (0.40-3.42)	0.766	*	
3 OAEs or more	0.44 (0.05-3.78)	0.455	*	

OR odds ratio, CI confidence interval

Table 3: Logistic regression model seizure frequency in epilepsy patients.

Variables	Univariable model		Multivariable model	
	b (95% CI)	P	b (95% CI)	P
Magnesium serum	-0.08 (-0.39-0.24)	0.627	0.01 (-0.33-0.35)	0.966
Dietary magnesium	0.00 (0.00-0.00)	0.497	*	
Age	-0.01 (-0.02-0.01)	0.492	-0.02 (-0.04-0.00)	0.042
Male versus female	0.11 (-0.35-0.57)	0.631	*	
Age at first awakening (years)				
<15 (ref)				
≥15	-0.34 (-0.82-0.14)	0.160	*	
Initial seizure frequency (months)				
≥2 (ref)				
0-1	0.43 (-0.08-0.94)	0.099	-0.53 (-1.19-0.14)	0.127
With status epilepticus	0.37 (-0.20-0.95)	0.201	*	
History of seizures fever	-0.10 (-0.58-0.37)	0.668	-0.46 (-1.11-0.18)	0.163
Family history	-0.20 (-1.08-0.67)	0.650	-0.75 (-1.75-0.25)	0.145
Sun exposure 3 days per week	-0.46 (-0.97-0.05)	0.075	-1.22 (-1.95-0.49)	0.001
Imaging				
Normal (ref)		0.011		
Abnormal	0.62 (0.14-1.10)		*	
Without the imagination	-0.03 (-0.69-0.62)	0.919	*	
EEG				
Abnormal versus normal	0.02 (-0.47-0.50)	0.947	*	
Total OAE				
1 OAE (ref)				

Continued.

Variables	Univariable model		Multivariable model	
	b (95% CI)	P	b (95% CI)	P
2 OAE	0.35 (-0.21-0.90)	0.215	*	
3 OAE or more	0.51 (-0.32-1.35)	0.224	*	

OR odds ratio, CI confidence interval

DISCUSSION

We found a significant relationship between seizures freedom and dietary magnesium intake, although this effect was small, with an odds ratio close to one but not with serum magnesium levels. However, these two factors do not appear to be related to seizure frequency. A similar phenomenon was demonstrated in the study by Akter et al and Han et al. They found that dietary magnesium level, but not serum magnesium, which has a significant relationship with insulin resistance and the risk of hypertension.[8,9]

The total magnesium content in the human body is around 1000 mmol or about 22.66 g. About 99% of the total magnesium in the body is in the cell, of which 60% is in the bone, 20% in the muscle, and about 20% in other tissues. About 1% of total magnesium is located in extracellular space, and around 0.3% is found in serum. We might not have assessed magnesium status adequately by using serum magnesium level and thus had no significant relationship with seizure freedom.[10,11]

Magnesium has a slow turn-over across the plasma membrane, and thus its concentration remains relatively constant over time. Reduced dietary magnesium intake results in a decrement in urinary magnesium excretion, without a fall in serum magnesium level. Therefore, there may be patients with lower total body magnesium levels not detected by existing tests.[12,13]

High dietary magnesium intake increases serum ionized magnesium. It can cross the blood-brain barrier and thus increase in neural magnesium concentration. Serum ionized magnesium is known to have a competitive antagonistic effect on NMDA receptors. It closes the ion channels through which sodium or calcium ions should pass and then prevents cell damage or excess excitability and improves seizure control.[4,14,15]

The dietary magnesium intake in this study was sufficient based on a person's recommended dietary allowance, but its effect on seizure freedom is low (OR almost one). A predecessor study by Peter et al demonstrated that magnesium supplementation in epilepsy people could reduce seizures' frequency. Additional magnesium supplementation seems necessary to get a more optimal control of attacks, but we do not do this in our patients.[4]

Statistically, we had a unique relationship; those with history of status epilepticus were five times more likely to have achieved seizure freedom. Previous studies found that the history of status epilepticus and its duration were associated with drug-resistant epilepsy occurrence. Our small number of samples may have led to this unique finding.[16-18] We found a significant relationship between the length of sun exposure and the frequency of seizures. Patient with epilepsy that was exposed to sunlight for more than 25 minutes for at least 3 days in a week experience 1-2 times lower seizures episodes per month than those who are less exposed. The effect of sun exposure is thought to be related to vitamin D levels. Inadequate sun exposure is a risk factor of low vitamin D levels by about 40%. Most of the enzymes involved in the metabolism of vitamin D require magnesium. Therefore, adequate magnesium intake is required so that vitamin D can provide optimal benefits.[19-23]

Limitations

This study has several weaknesses; we did not check the magnesium loading test, which is the gold standard for magnesium measurement. As a micronutrient, a 24-hour recall method is less suitable for assessing dietary magnesium intake. We also did not check vitamin D levels in this study.

CONCLUSION

Dietary magnesium intake was associated with seizure freedom. In this study, we further enhance the importance of magnesium for epileptic patients. Regardless of its serum levels, those who routinely had more dietary magnesium intake will likely to have benefits in controlling seizure. Further study to define the exact dosage of magnesium supplementation is encouraged.

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