Serum Magnesium Level in Children with Epilepsy Attending Qena University Hospital, Upper Egypt

Hala M. Sakhr[a], Mohammed H. Hassan [b], Asmaa E. salah [a*], Ali H. Bakry [a]
a Department of Pediatrics, Faculty of Medicine, Qena University, Qena, Egypt.
b Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Qena University, Qena, Egypt.

Abstract

Background: Magnesium (Mg) is the body's fourth most abundant cation. It is an essential mineral associated with the development of various neurological illnesses and is related to neuronal excitation mediated by various neurotransmitters.

Objectives: To assess serum Mg levels in children with epilepsy in relation to the type of convulsions and electroencephalography (EEG) changes.

Patients and methods: A case-control study was conducted on 100 participants, including 50 epileptic children and 50 healthy matched subjects, between the ages of 2 and 18 years. The cases were categorized according to the type of convulsion and EEG findings. Serum Mg, routine laboratory tests, and an interictal EEG were performed.

Results: Fifty epileptic children with a mean age of 7.61 ± 3.27 years. Children with epilepsy had a higher positive family history of epilepsy than the control group. The patients had lower haemoglobin, sodium, and calcium levels than the healthy group. Serum Mg levels exhibited a significant decrease in cases (2.05 ± 0.3 mg/dl) compared to controls (2.2 ± 0.16 mg/dl), with 22% of the patients having hypomagnesemia while hypomagnesemia was present in only 2% of the control group. Serum Mg was also significantly lower in patients with focal epileptic discharges and cerebral dysrhythmia on EEG findings compared to patients with generalized epileptic discharges. A significant negative correlation was found between serum Mg levels and heart rate, platelet count, and temperature, and a positive correlation with haemoglobin level.

Conclusion: Mg levels play an important role in the pathogenesis of epilepsy.

Keywords: Epilepsy; Serum magnesium; Children; Qena.
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***Correspondence**: Asmaaesmailsalah@gmail.com
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Introduction

Epilepsy is a dangerous neurological disease that is defined by the occurrence of repeated, periodic, and unpredictable epileptic seizures, which may be caused by an imbalance in the excitatory and inhibitory pathways within the central nervous system (CNS). It is one of the most common and severe neurological conditions, affecting over 70 million people globally **(Milligan, 2021).**

The precise pathogenesis and mechanism of epileptogenesis are still unknown; however, genetic, congenital, and acquired factors have been implicated (**Fisher et al., 2014**).

Magnesium (Mg2+) is the second most abundant intracellular cation after potassium and plays a part in several enzymatic reactions. It maintains different physiological functions such as heart rhythm, blood pressure, impulse conduction, and muscle contraction. It acts as a blocker of calcium channels located in the N-methyl-D-aspartate (NMDA) receptor, thus inhibiting excitotoxicity. It also has anti-inflammatory and antioxidant properties (**Mathew and Panonnummal, 2021**).

The concentration of Mg in the central nervous system is related to neuronal excitation, facilitated by several neurotransmitters, especially glutamate **(Chen et al., 2023)**. Deficiency of extracellular Mg^{2+} leads to neuronal hyper-excitation due to over-activation of NMDA receptors (**Li and Toffa, 2023**). Additionally, Mg^{2+} can regulate the gamma-aminobutyric acid $_A$ ($GABA_A$) receptor, which has an inhibitory function. Furthermore, low Mg^{2+} causes enhanced calcium influx, which increases the release of glutamate in the CNS and so leads to excitotoxicity (**Ayyaswamy, 2023**).

Magnesium exerts several neuroactive effects on a molecular, cellular and systemic level. The central effects of magnesium include the antidepressant, anxiolytic, anesthetic, analgesic, antimigraine, anticonvulsant, antiepileptic and neuroprotective effects. It has an overall stabilizing effect on cell membranes of neurons. Electrophysiological data shows that Mg2+ ion impacts the regulation of the intrinsic properties of the neuronal cell membrane (excitability, conductivity, and resistance), and carries out complex modulation of neuronal electrical activity through its synaptic and non-synaptic effects, i.e. Mg2+ effects on ion channels, transporters and pumps, and receptors in the cell membrane. Mg suppresses chemical synaptic neurotransmission by binding to voltage dependent Ca2+ channels of presynaptic nerve endings, hence, suppressing the release of neurotransmitters from central as well as peripheral synapses. In addition, extracellular Mg2+ ions block N-methyl-D-aspartate (NMDA) ionotropic glutamate receptors in a voltage-dependent manner**. (Stanojević et al., 2023)**

The goal of our research was to assess the role of Mg in the pathophysiology of epilepsy and its relationship with epilepsy type and EEG findings.

Patients and methods

Study design

Case-control research with 100 participants included 50 paediatric patients with epilepsy from the Paediatric Department and Neuropediatric Outpatient Clinic at Qena University Hospital, as well as 50 healthy-matched controls. The trial ran from December 2022 to June 2023.

Inclusion criteria:

All patients aged between 2 and 18 years who presented with epilepsy, which was explained as the occurrence of at least two unprovoked seizures occurring more than 24 hours apart **(Fisher, 2015)**.

Exclusion criteria:

Children less than 2 years of age and those older than 18 years at the time of presentation were excluded. Febrile patients and those suffering from other systemic, mental, or psychiatric diseases, as well as metabolic abnormalities, were also excluded from the study.

Sample size:

This study is based on the study conducted by (Sarker et al., 2022). Epi Info STATCALC was used to compute the sample size based on the following assumptions. - 95% two-sided confidence, with 80% power. The odds ratio was calculated to be 1.115 with a 5% error

using the calculation below: N equals [DEFF*Np(1-p)]/ [(d2/Z21-α/2*(N-1) + p*(1-p)]

The final maximum sample size calculated from the Epi-Info output was 92. Thus, the sample size was raised to 100 participants to account for possible dropouts during follow-up.

participants will be divided into 2 groups: Group A: 50 epileptic children and Group B: 50 healthy matched subjects.

Clinical evaluation

All patients included in the study were subjected to a detailed history, including personal data (age, sex, residence, and socioeconomic status), type of seizures, post-ictal symptoms, seizure frequency, prenatal, developmental, vaccination, and medical history. Physical examination by recording the patient's vital signs, including heart rate, respiration rate, temperature, and systolic and diastolic blood pressure. A recording of the patient's weight and length was done, and the body mass index was calculated. Cardiac, chest, and abdominal examination to exclude the presence of congenital anomalies or other associated chronic diseases. A comprehensive neurological examination was done to exclude other neurological disorders.

Laboratory work-up

Routine laboratory work-up was done, including complete blood count (CBC), liver and renal function tests, and serum electrolytes. Serum magnesium was measured using commercially available colorimetric assay kits. All were supplied by Spectrum Diagnostics, Egypt (catalogue number 285 002). All assays were performed using a spectrophotometer (Chem-7, Erba Diagnostics Mannheim GmbH, Germany). Normal serum Mg level is 1.8-2.06 mg/dl (**Fiorintini et al., 2021**).

Electroencephalogram evaluation

An Interictal electroencephalogram was done to assess the abnormality and type of seizure, using an electroencephalograph (NIHON KOHDEN, EEG-1200 K, EUROPE GmbH-Rosbach-Germany).

Ethical approval

All subjects included in the study signed a written informed consent before their inclusion in this study, and the institutional ethical committee of the Faculty of Medicine, Qena, approved the study

Ethical approval code: (IRB NO. SVUMED-PED025-1- 22-12-528).

Statistical analysis

Data was analyzed using the Statistical Package for Social Sciences (SPSS) application (version 24). Qualitative variables were recorded as frequencies and percentages and compared using the chi-square test. Data Normality distribution was evaluated by Kolmogorov–Smirnov test. Quantitative measurements were presented as means ± standard deviation (SD) and compared using the student t-test. Pearson Correlation between various variables will be made as indicated. P-values < 0.05 will be considered significant.

Results

The mean age of cases included in our study was 7.61 ± 3.27 years, which exhibited a non-significant difference with the mean age of controls (7.41 ± 1.27 years). Similarly, there was no significant difference between both groups regarding sex distribution. Compared to the control group; cases had a significantly positive family history for epilepsy (46%) than controls (2%). Parental consanguinity was detected in 24 cases (48%) and 20 controls (40%).

Regarding vital signs, we found a significant decrease in heart rate and a significant increase in the respiratory rate in cases compared to controls, with a mean of 101.1 ± 10.09 beats/minute and 15.72 ± 1.79 breaths/minute, however, controls had a mean of 104.88 ± 5.56 beats/minute 14.98 ± 1.66 breaths/minute. Non-significant difference was found as regards blood pressure parameters and temperature (p = 0.6) as shown in **Table 1.**

The patient group had an average seizure duration of 9.48 ± 6.75 minutes and a frequency of 15.98 ± 25.5 incidents in the past two years. 28 patients (56%) had a history of status epilepticus, while 24 patients (48%) had concomitant febrile convulsions. Seizure type was identified as focal onset seizure in 8 cases

(16%) and generalised onset seizure in 42 patients (84%). EEG abnormalities were seen in 45 (90%) of the cases investigated. Laboratory results **(Table 2)** demonstrate that cases had a decreased mean hemoglobin (9.75 ± 1.05 g/dl vs. 11.12 ± 1.15 g/dl in the control group). However, our data showed no significant variations in white blood cell or platelet counts between patients and controls. Serum sodium (Na) levels decreased significantly in the cases group (1.39.56 ± 3 mmol/L) compared to the control group (141.48 ± 3.94 mmol/L) (p = 0.0074). Serum ionized calcium (Ca) levels were significantly lower in patients compared to controls (p = 0.038), with the cases group having a mean of 1.11 ± 0.1 mmol/L and the controls having 1.15 ± 0.09.

Serum potassium (K), serum creatinine, and liver enzymes (ALT and AST) showed no significant differences among both groups. In our study, serum Mg exhibited a significant decrease in cases in comparison with the control group with 22% of the cases having hypomagnesemia, while hypomagnesemia was present in only 2% of the control group (p = 0.002), as shown in **table 3**. However, there was no significant difference in serum magnesium or hypomagnesemia between focal-onset seizures and generalized-onset seizures. Serum magnesium was significantly lower in patients with focal epileptic discharges and cerebral dysrhythmia on EEG compared to generalized epileptic discharges (P = 0.04).

Table 1. Clinical data of studied groups

Quantitative Variables (mean ± SD)	Cases (N = 50)	Controls (N = 50)	P-Value
Age (years)	7.61 ± 3.27	7.41 ± 1.27	0.688 (t)
Sex N (%)			
Male	22 (44%)	20 (40%)	0.685 [x]
Female	28 (56%)	30 (60%)	
Residence N (%)			
Urban	24 (48%)	25 (50%)	0.84 [x]
Rural	26 (52%)	25 (50%)	
Family History of epilepsy N (%)	23 (46%)	1 (2%)	<0.0001* [x]
Parental consanguinity N (%)	24 (48%)	20 (40%)	0.420 [x]
Weight (kg)	22.11 ± 10.01	23.92 ± 10.87	0.388 (t)
Height (cm)	112.64 ± 20.2	117.14 ± 19.84	0.264 (t)
Blood Pressure			
Systolic (mmHg)	96.2 ± 7.39	96.38 ± 7.83	0.9 (t)
Diastolic (mmHg)	70.1 ± 7.91	68.9 ± 10.6	0.523 (t)
Heart Rate (Beat/min)	101.1 ± 10.09	104.88 ± 5.56	0.022 * (t)
Temperature (°C)	36.9 ± 0.39	36.86 ± 0.37	0.60 (t)
Respiratory rate (breath/min)	15.72 ± 1.79	14.98 ± 1.66	0.034 * (t)

*: significant; t: student's t- test; x: Chi-square test.

Table 2. Laboratory data in the studied groups

Variable (mean ± SD)	Cases (N = 50)	Controls (N = 50)	P. Value
Complete blood count			
Haemoglobin (g/dl)	9.75 ± 1.05	11.12 ± 1.15	<0.0001* (t)
White blood cells (x 10^3/mm)	6.9 ± 1.95	7.02 ± 2.1	0.767 (t)
Platelets (x10^3/mm)	290.49 ± 77.86	274.8 ± 44.43	0.219(t)
Kidney function tests			
Serum creatinine (mg/dl)	0.6 ± 0.12	0.64 ± 0.1	0.073 (t)
Electrolytes			
Serum Na (mmol/L)	139.56 ± 3	141.48 ± 3.94	0.0074 * (t)
Serum K+(mmol/L)	4.2 ± 0.38	4.29 ± 0.41	0.257 (t)
Ionized Ca (mmol/L)	1.11 ± 0.1	1.15 ± 0.09	0.038* (t)
Liver function tests			
ALT(U/L)	37 ± 7.88	37.02 ± 7.56	0.989 (t)
AST(U/L)	31.92 ± 7.18	30.32 ± 3.49	0.160 (t)

t: student's t-test; *: significant, Na: sodium; k: potassium; ca: calcium; ALT: alanine transaminase; AST: aspartate transaminase.

Table 3. Serum magnesium level among the different subgroups of the studied cases

Variable (mean ± SD)	**Cases (N = 50)**	**Controls (N = 50)**	**P-Value**
Serum Mg (mg/dl)	2.05 ± 0.3	2.2 ± 0.16	0.0025 * (t)
Cases with hypomagnesemia N (%)	11 (22%)	1 (2%)	0.002* [x]
	Cases with Focal onset seizure (N = 8)	**Cases with Generalized onset seizure (N = 42)**	**P-Value**
Serum Mg (mg/dl)	2.05 ± 0.26	2.04 ± 0.31	0.924 (t)
	Normal EEG patients (N = 5)	**Abnormal EEG patients (N = 45)**	**P-Value**
Serum Mg (mg/dl)	2.1 ± 0.41	2.04 ± 0.29	0.765 (t)
	Focal Epileptic Discharge and Cerebral dysrhythmia on EEG (N = 15)	**Generalized Epileptic Discharge on EEG (N = 30)**	**P-Value**
Serum Mg (mg/dl)	2.07 ± 0.25	1.8 ± 0.21	0.04* (t)

*: significant; t: student's t- test; x: Chi-square test; Mg: magnesium.

A significant negative correlation was identified between serum magnesium levels and HR (r= -0.378, p = 0.0068) in all the studied cases **(Fig 1A)**, and in cases with abnormal EEG findings (r = -0.467, p= 0.0012) **(Fig 1B)**.

Additionally, there was a significantly positive correlation between serum creatinine and serum magnesium (r = 0.356, p = 0.0112) among all study cases and among cases with abnormal EEG findings (r = 0.310, p = 0.0385) as shown in **Fig 2A** and B respectively.

Among abnormal EEG cases, we also noted a negative correlation between PLT and magnesium levels (r = -0.324, p = 0.0298), as shown in **Fig (3)**.

A- B-

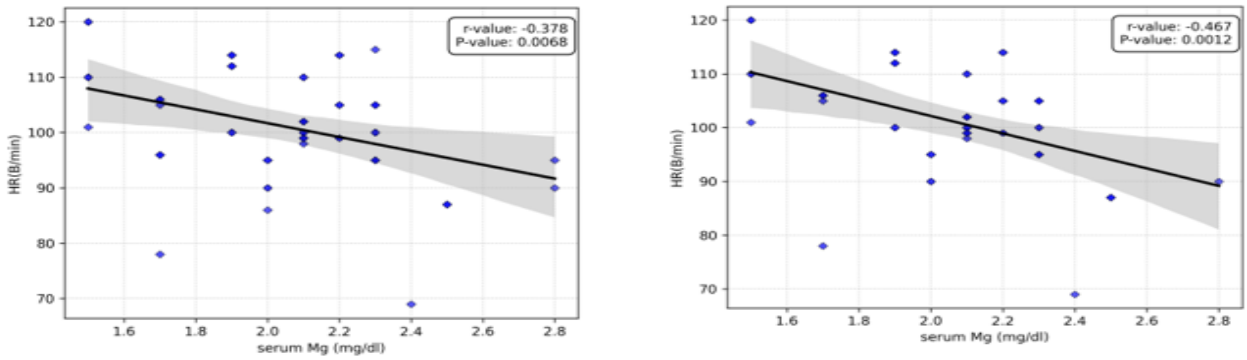

Fig 1. Correlation between serum Mg (mg/dl) and HR (b/min) among all the studied cases (A) and among cases with abnormal EEG findings (B).

A- B-

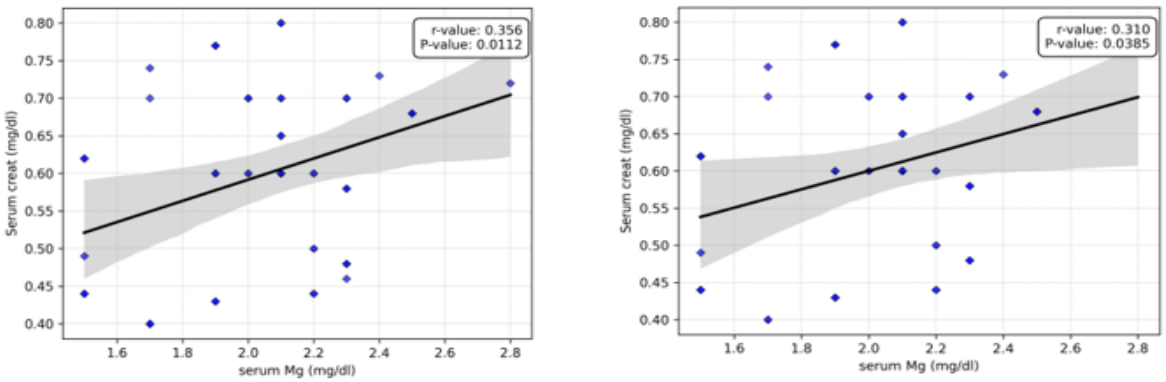

Fig 2. Correlation between serum Mg (mg/dl) and serum creatinine (mg/dl) among all studied cases (A) and cases with abnormal EEG findings.

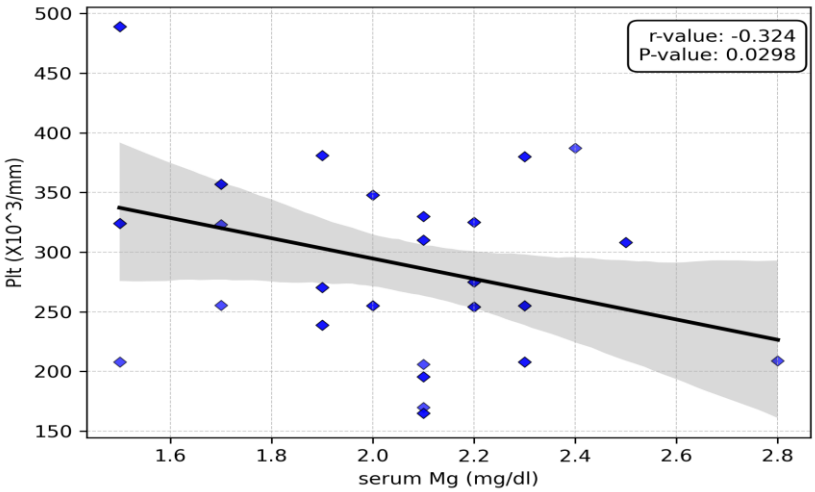

Fig 3. Correlation between serum Mg (mg/dl) and PLT (X10^3/mm) among cases with abnormal EEG.

Discussion

Magnesium ions exist in greater concentrations in the intracellular fluid (second to the K+ ion) than in the extracellular fluid. Its intracellular and extracellular concentrations are controlled by the cell membrane ion channels, as well as by the control mechanisms regulating its storage in different cell organelles. Magnesium homeostasis is essential for preserving the general state of health. Magnesium acts as a cofactor for many enzymes involved in maintaining and regulating many physiological processes. It also acts as a signaling molecule, reducing neuronal excitotoxicity and maintaining the level of other ions such as potassium and calcium (**Mathew and Panonnummal, 2021**).

Magnesium deficiency was shown to be linked to many brain-related diseases, including migraine, stroke, neurodegenerative diseases, depression, and epilepsy. Reports suggest that administering magnesium supplements can rectify blood-brain barrier breakdown, edema, and excitotoxicity associated with these neurological diseases (**Haldar et al., 2021**).

In the current study, 50 cases of epilepsy with a mean age of 7.61 ± 3.27 years, and males represent 44% of them. **Colebunders et al. (2016)** showed similar results regarding sex distribution between cases and controls (males made up 47% of the case population) but with older age of the cases.

In our study, epileptic children had a higher positive family history of seizures than controls, but parental consanguinity showed no significant difference between both groups. **Chentouf et al. (2015)** found a significantly increased positive family history and parental consanguinity in cases compared to controls, especially first-degree consanguinity as well as first-degree relatives' affection. A study by **Saygi et al. (2014)** found that neither a positive family history of seizure disorder nor parental consanguinity constituted significant predictors of intractable epilepsy. **Hunza et al. (2011)** did not find a link between epilepsy and parental consanguinity in a group known to have high rates of consanguineous marriage, even though 50% of cases had a positive family history of epilepsy. **Ünver et al. (2015)** demonstrated that a positive family history of epilepsy was found in 33% of patients, and the consanguinity rate was 27.8%.

In our study HR exhibited a borderline significant decrease in cases compared to controls. **Karabulut et al. (2023)** showed similar results. On the other hand, **Noori et al. (2020)** demonstrated a significant increase in heart rate in epileptic children compared to controls, 129.64 ± 27.63 b/m and it was 108.78 ± 26.01 b/m respectively. Autonomic dysfunction, especially sympathetic over activity, occurs in most forms of epilepsy. Heart rate changes have been linked to sudden unexplained death in epilepsy (SUDEP), which is the primary cause of mortality in several epilepsy populations **(Myers et al., 2018)**.

In the current study, the mean respiratory rate (RR) was significantly higher in patients than in controls ($p = 0.034$). It was 15.72 ± 1.79 breaths per minute (b/m), and controls had a mean of 14.98 ± 1.66. Contradictory to our findings, **Jansen et al. (2013)** studied the RR changes in children with temporal lobe epilepsy and showed a shift of RR toward lower frequencies in patients with temporal lobe seizures compared to control subjects.

In our study, there were no significant differences between patients with epilepsy and controls in terms of systolic and diastolic blood pressure or temperature. These results were in line with the results of **Hamed et al. (2024)**.

Our study revealed that cases had significantly lower mean Hgb than controls. These results were in line with **Sharif et al. (2016) who** reported iron deficiency anemia as a risk factor for febrile convulsions, as it was found in 45% of the convulsion group and 22% in the group with fever without convulsions. In line with our findings, the study conducted by **Fallah et al. (2014)** involving 150 children distributed equally into three groups (febrile seizures, afebrile seizures, and control). They revealed that both the febrile seizures group and the afebrile seizures group exhibited lower Hgb

levels compared to the control group. This suggests a potential association between seizures and decreased hemoglobin levels in children. However, **Zhu et al. (2018)** found no significant difference between epileptic patients and controls regarding Hgb level, WBCs, platelets, as well as liver functions.

In the current study, serum sodium (Na) showed a significant decrease in the cases group compared to the controls ($p = 0.0072$). In contrast, **Tolou-Ghamari et al. (2013)** found no significant differences in serum levels of sodium between children on antiepileptic drugs and controls. On the other hand, **Ristić et al. (2014)** observed significantly increased sodium levels in patients with drug-resistant epilepsy compared to controls.

Conversely, serum ionized calcium (Ca) levels were significantly difference between cases and controls ($p = 0.038$). This was in line with the findings by (**Prasad et al., 2014; Karabulut et al., 2023)**, In contrast, **Tombini et al. (2018)** increased calcium levels were observed in patients with epilepsy.

In our study, serum potassium (K) was not significantly different between the two groups ($p = 0.257$). The liver enzymes (ALT and AST) showed no significant differences between the groups.

Karabulut et al. (2023) found no statistically significant differences between cases and controls in Na+, K+, Mg, and WBC counts. The study by **Adedapo et al. (2020),** found no statistically significant difference in serum ALT or AST in epileptic and non-epileptic children.

Considering the results of our study, serum Mg levels exhibited a significant decrease in cases (2.05 ± 0.3 mg/dl) compared to controls (2.2 ± 0.16 mg/dl). In addition, 22% of the patients in the cases group exhibited hypomagnesaemia, compared to only 2% in the control group ($p = 0.002$). We found a significant negative correlation between serum magnesium levels and HR ($r = -0.467$, $p = 0.0012$).

Various research found conflicting results on serum Mg in epileptic individuals. In line with our findings, Suh et al. (2018) revealed lower serum magnesium levels in epileptic patients. **Guo et al. (2023)** showed that higher serum magnesium levels were associated with a lower risk of overall epilepsy. In International League Against Epilepsy (ILAE), higher serum magnesium levels were found to be associated with a reduced risk of focal epilepsy. However, the study by **Karabulut et al. (2023)** found no statistically significant differences in serum Mg levels between cases and controls. Furthermore, **Zhu et al. (2018)** found no statistically significant difference in serum Mg levels between patients with epilepsy and healthy controls, but they found a significant negative correlation between HR and serum magnesium levels ($r = -0.378$, $p = 0.0068$). **Bharathi and–Chiranjeevi, 2016** showed that a higher percentage of patients with generalized seizures were hypomagnesemic than those with focal seizures.

Khosroshahi et al. (2015) found no significant correlation between fever and magnesium levels in serum or CSF. However, **Suh et al. (2018)** reported lower magnesium levels in epileptic patients suffering from febrile seizures. **Chen et al. (2016)** reported that hypomagnesemia contributed to the occurrence of afebrile seizures in all their cases.

Hypomagnesaemia can also decrease serum calcium levels by influencing parathyroid hormone synthesis or secretion. Furthermore, hypocalcemia, alongside hypomagnesemia, can cause neuronal membrane hyper-excitability, which is closely related to seizures in children as well as adults **(Prasad et al., 2014)**. The major clinical findings of hypomagnesemia consist of neuromuscular irritability, CNS hyper excitability, and cardiac arrhythmias. Seizures, often generalized tonic-clonic, can occur in newborns and adults in conjunction with severe hypomagnesemia (**Castilla-Guerra et al., 2006**).

In a randomized open-label study, the addition of intravenous magnesium supplementation to adrenocorticotropic hormone, increased seizure-free rates at 4–28 weeks compared to adrenocorticotropic hormone monotherapy

among children with infantile spasms (**Zou et al., 2010**).

Abdelmalik et al. (2012) showed that magnesium supplementation could decrease seizure days per month for patients with pharmacoresistant epilepsy. There are studies showing that convulsive seizures are better controlled with adequate magnesium supplementation. It was also shown that parenterally administered magnesium has efficiently controlled convulsions in many epileptic encephalopathies in adults and children (in eclampsia, uremia, porphyria, febrile seizures, and infantile spasms); in addition, it helps control the status epilepticus **(Yuen et al., 2012)**. Daily administration of 450 mg of magnesium in adult epileptic patients has been shown to reduce the need for anti-epileptic drugs. **Prousky (2014)** showed that oral magnesium supplementation in epileptic patients can lead to a reduction in the frequency of seizures.

Conclusion

Hypomagnesemia was detected in 22% of the cases studied. Epileptic children have lower serum magnesium levels than healthy children, and patients with focal epileptic discharges and cerebral dysrhythmia on EEG had significantly lower Mg levels than patients with generalized epileptic discharges, indicating that Mg levels play an important role in the pathogenesis of epilepsy. Therapeutic magnesium supplementation has to be established by further interventional studies.

Study limitations

The ongoing research is susceptible to a range of defects and constraints. One crucial determinant that leads to the diminished statistical estimates of connection with the measured outcomes is the limited sample size of people included in the study. The generalizability of the study results to pediatric patients residing in different regions of the nation is hindered by the exclusive treatment of all subjects at Qena University Hospital (QUH). Hence, it is essential to do more studies on a broader scope and across diverse locations. The incorporation of more data about clinical evaluation of patients will augment our findings.

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