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PROSPECTIVE OBSERVATIONAL STUDY OF SERUM MAGNESIUM LEVELS IN MIGRAINE PATIENTS DURING THE ICTAL AND INTERICTAL PHASES

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ABSTRACT

Background and objectives: Migraine is among the most common headaches, with a 15% worldwide incidence. It is distinguished by neurovascular dysfunction and recurring headaches. Magnesium (Mg), as a controller of synaptic activity, is hypothesised to play a role in migraine pathogenesis. The cerebral cortex's hyperexcitability has been identified as a key feature in the pathophysiology of migraine, and magnesium (Mg) is a known neuronal excitability regulator. To evaluate the serum magnesium levels of migraine patients during and between attacks to those of healthy controls.

Methods: Sixty migraine patients who met the inclusion criteria and the equal number of healthy controls were enrolled in the study. For the diagnosis of migraine, the International Classification of Headache Disorders, 3rd Edition, 2013 (ICHD-III) criteria were applied.

Result: The mean serum magnesium levels of migraine patients throughout the interictal phase were significantly lower than those of healthy controls (1.849 0.135 vs 2.090 0.205, P 0.001, statistically significant). During attacks, the mean serum magnesium concentration was substantially lower than between attacks (P = 0.003, 1.822 0.149 vs 1.849 0.135, respectively). In migraine patients, serum magnesium levels exhibited an inverse linear relationship with attack frequency.

Conclusion: The relatively low serum magnesium levels in migraine patients compared to healthy controls and the inverse relationship between serum magnesium levels and the frequency of migraine attacks suggest that magnesium plays a significant role in the pathogenesis of migraine and may be a viable therapeutic option.

Keywords: Magnesium, migraine, neurovascular, pathophysiology.

INTRODUCTION

Migraine constitutes one of the most widespread and disabling diseases; it is categorised by recurrent episodes of moderate or severe, unilateral, pulsating headache that are usually affected by aggravating side effects such as nausea, vomiting, photophobia, and phonophobia; approximately one-third of patients experience aura symptoms during some of their migraine attacks [1,2]. Acute medication (abortive or symptomatic treatment) is intended to stop severe attacks, whereas preventative treatment (prophylactic treatment) is intended to lessen the intensity and frequency of migraine attacks. Acetaminophen, aspirin,

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and nonsteroidal anti-inflammatory medicines (NSAIDs), as well as ergot analogues alone or in association with caffeine, have traditionally been the first-line therapies for the acute treatment of patients with mild to moderate symptoms. Individuals with moderate or severe discomfort are advised to take triptans alone or in combination with NSAIDs. In reality, triptans, also known as 5-HT1B/1D receptor agonists, are the primary treatment for severe migraines [3,4,5].

In addition, the triptan discontinuation rate was considerable, ranging from 55.2% to 81.2%. Recent research, however, have concentrated on innovative formulations of triptan treatment, such as the delivery of medicines via non-oral channels, such as the subcutaneous (SC) (DFN-11: 3 mg doses of SC sumatriptan) and intranasal routes (DFN-02: a nasal spray of sumatriptan 10 mg and a permeation-enhancing excipient). Patients with high blood pressure, cardiovascular disease, or cerebrovascular illness should not use triptans due to their 5-HT1B-mediated vasoconstrictive action [6,7]. Understanding the etiology of migraines has led to the development of serotoninergic agonists without vasoconstrictive effects; these agonists target the 5-HT1D and 5-HT1F receptors. Regrettably, a phase II trial investigating the efficacy of 5-HT1D agonists failed to fulfil the primary endpoint; therefore, further development was halted. Lasmiditan, the first drug in its class to demonstrate statistically significant efficacy, was approved by the Food and Drug Administration (FDA) in October 2019 [6,7,8].

This study aims to compare the serum magnesium levels of migraine patients during and between attacks to those of healthy controls.

MATERIAL AND METHODS:

This was a prospective observational study comparing the serum magnesium levels of migraine patients during as well as between attacks to those of healthy controls at Government General Hospital, Nandyal, AP from January 2021 to January 2022. Sixty migraine patients who met the inclusion criteria were included in the trial. Migraine was diagnosed using the International Classification of Headache Disorders, 3rd Edition, 2013 (ICHD-III) criteria. Healthy controls were recruited from the hospital staff, patient attendants, and the general public. Before participating in the study, all patients and controls gave written informed consent.

In migraine cases, the age of onset, length of disease, number of migraine attacks per month, average duration of headache episodes, triggering factors, aura and its kind, location, nature, severity, onset to peak latency, and accompanying symptoms were collected in detail. Using a visual analogue scale ranging from 1 (little pain) to 100 (maximal pain), the degree of pain during migraine attacks was measured [8,9]. Migraineurs' blood was drawn in the morning after a minimum of 8 h of fasting, once during their headache attack (or within 24 h following headache), and then at least 7 days after their previous migrainous headache (interictal phase). After a minimum of 8 hours of fasting, blood samples from the controls were drawn in the morning. In the biochemistry laboratory, serum Mg levels were estimated using a colorimetric assay with Vitros Chemistry Products slides.

The obtained data included both categorical variables (numbers and percentages) and continuous variables (mean standard deviation and median). The Kolmogorov-Smirnov test was employed to examine the data's normality. Unpaired t-test or Mann-Whitney U-test The U test was utilised to compare quantitative factors across the two groups, whereas the paired

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t-test/Wilcoxon test was utilised to compare quantitative variables throughout the ictal and interictal phase [9,10]. The Chi-square test and Fisher's exact test were utilised to compare qualitative data. A P value 0.05 was maintained as statistically significant. The data were analysed using the MS EXCEL spreadsheet and version 21.0 of the statistical software for social sciences (SPSS).

Inclusion criteria:

1. Adult males and females between the ages of 18 and 45 were diagnosed with migraine based on ICHD-III criteria.
2. Age (2 years), healthy controls of the same gender and body mass index (BMI).

Exclusion criteria:

Patients with

1. Non-migrainous headache
2. Chronic migraine (headache 15 days per month) are evaluated.
3. Recognised cases of diabetes mellitus, arterial hypertension, dyslipidemia, head injury, chronic renal disease, gastrointestinal diseases including malabsorption syndrome and antacid abuse, thyroid issues, hyper/hypoparathyroidism
4. History of epilepsy or stroke and coronary heart disease
5. BMI 18 kg/m2 or >35 kg/m2
6. Any drug addiction and nicotine dependency
7. Pregnancy or lactation
8. Drug use including hormonal medicines, calcium, and magnesium supplements during the previous three months, diuretics, aminoglycosides, acetazolamide, and amphotericin B.

RESULTS:

Table 1: General characteristics of the migraine cases and healthy controls

Characteristics	Migraine cases	Controls	P
Mean age (in years)	28.92±5.92	28.52±5.57	0.687
Females (% age)	70%	70%	1
BMI (kg/m^2)	22.29±1.83	22.37±1.66	0.523

There was no significant difference in the distribution of age, gender, or BMI between the migraine and control groups.

Table 2: Distribution of migraine cases according to disease duration, frequency of attacks, presence of aura, pain severity, and associated symptoms

Distribution factor	**Distribution criteria**	**Cases**		**Mean value**
		n	**%**	
Duration (years)	<5	39	65.0	4.4±2.24
	≥5	21	35.0	
Frequency (attacks/months)	<4	35	58.3	3.26±1.71
	≥4	25	41.6	

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Aura	Absent	37	61.6	
	Present	23	38.3	
Pain Severity (As per VAS Score)	Mild	07	11.6	
	Moderate	45	75	
	Severe	08	13.3	
Associated symptoms	Photophobia	38	63.3	
	Phonophobia	46	76.6	
	Nausea	48	80	
	Vomiting	06	10	

70 percent of the participants were females aged 30 years with a normal BMI. 37 out of 60 migraine cases lacked aura, and the majority had a disease duration of less than 5 years.

Table 3: Relation of serum magnesium (mg) with various factors in migraine cases and controls

Factor	**Groups**	**Cases (in between attacks)**			**Cases (during attacks)**			**Controls**		
		Serum Mg (Mg/dl)		**P**	**Serum Mg (Mg/dl)**		**P**	**Serum Mg (Mg/dl)**		**P**
		Mean	**±SD**		**Mean**	**±SD**		**Mean**	**±SD**	
Age (yrs)	**<30**	1.858	0.139	0.647	1.831	0.143	0.643	2.129	0.189	0.115
	≥30	1.840	0.133		1.811	0.158		2.036	0.218	
Sex	**M**	1.862	0.148	0.647	1.836	0.165	0.639	2.093	0.143	0.954
	F	1.843	0.130		1.815	0.143		2.089	0.230	
BMI	**<22.9**	1.844	0.134	0.658	1.823	0.152	0.896	2.097	0.214	0.755
	≥22.9	1.863	0.141		1.817	0.148		2.078	0.194	
Duration	**<5**	1.851	0.126	0.925	1.821	0.147	0.980			
	≥5	1.847	0.154		1.822	0.158				
Frequency	**<4**	1.930	0.099	<0.001	1.919	0.098	<0.001			
	≥4	1.729	0.079		1.676	0.074				
Aura	**Absent**	1.846	0.137	0.814	1.818	0.156	0.803			
	Present	1.856	0.135		1.829	0.139				

There was no correlation between serum magnesium levels and age, sex, BMI, disease duration, aura presence, or aura absence; however, the mean serum magnesium levels in migraine cases with frequency 4/month were considerably lower than in migraine cases with frequency 4/month (P 0.001).

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DISCUSSION:

The current investigation revealed that throughout the interictal phase, the mean serum magnesium levels in migraine patients were significantly lower than in healthy controls (P 0.001). Among migraine patients, serum magnesium levels were considerably lower during the attack phase compared to the interictal period. As a neuronal excitation regulator, magnesium plays a crucial role in the aetiology of migrainous migraines [10,11]. Mg concentration is engaged in numerous pathophysiologic pathways, including cortical spreading depression, central sensitization, and activation of the trigeminovascular system, via its effect on numerous neurotransmitters and receptors associated with migraines. Numerous earlier investigations have demonstrated that migraineurs have decreased serum magnesium concentrations during interictal phases compared to healthy young adults [12,13]. There is a scarcity of literature regarding the shift in serum magnesium levels between the interictal period and migraine attacks. Ramadan et al. discovered that brain Mg (as assessed by 31-Phosphorus Nuclear Magnetic Resonance Spectroscopy) in migraine patients during an attack was significantly lower than in control subjects. In his study, Sarchielli et al. also found a drop in the mean serum magnesium levels of migraine patients during the attack period compared to the interictal period [14,15]. In comparison, Samaie et al. showed no variation in serum Mg concentrations between migraine attacks and interictal phase. Mauskop et al. reported a significant prevalence of magnesium insufficiency during monthly migraines, indicating that magnesium deficiency plays a role in the pathophysiology of menstrual migraines. Hormonal activities on Mg could be the cause of menstrual migraines, and intravenous treatment of Mg can help stop menstrual migraine attacks, according to a theory [15,16].

Stress, due to lack of sleep, and starvation may precipitate non-menstrual migraine attacks through similar pathways involving magnesium metabolism. The mean serum Mg levels in migraine cases with a recurrence of 4/month were significantly lower than in migraine cases with a frequency of 4/month (P 0.001), suggesting that serum Mg may play a role in defining sensitivity of individuals to migrainous headaches and threshold of migraine attacks due to its role in multiple mechanisms of migraine pathogenesis [16,17]. A number of previous research have similarly found an inverse connection between serum magnesium levels and the frequency of migraine attacks. Existing pharmacological treatments for migraines are only helpful in a subset of people, and there is a need for more effective treatments. Mg's significance in establishing the threshold for migraine attacks and its involvement in the pathophysiologic mechanisms of migraine have lately become obvious, making it a viable therapeutic agent for migraine [17,18].

Our research was limited by the fact that we measured total serum magnesium rather than the biologically active ionised form. Although many mechanisms have been proposed to explain the link between magnesium and the migraine physiologic threshold, more investigations at the cellular and molecular levels are required to validate this association and explore the possibility of magnesium as a migraine therapeutic.

CONCLUSION:

Serum magnesium showed significant decrease in migraine patients than in healthy controls, and there was an inverse correlation between serum magnesium levels and the recurrence of

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migraine attacks, suggesting that magnesium plays a key role in the pathogenesis of migraine and it could be explored as a therapeutic strategy.

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