

A STUDY ON SIGNIFICANCE OF SERUM MAGNESIUM IN MIGRAINE

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ABSTRACT

BACKGROUND

Magnesium has been implicated as a key molecule in several mechanisms of migraine pathogenesis. Central neuronal hyperexcitability is suggested to be the pivotal physiological disturbance predisposing to migraine. In this study, the role of serum magnesium in defining the physiologic threshold for migraine and modulating the various mechanisms of migraine genesis was searched for.

MATERIALS AND METHODS

The study enrolled adult migraine patients of age 18 to 40 years (41 females and 29 males) with and without aura and healthy controls of the same age group. Serum magnesium levels measured in the interictal period (between attacks) in cases were compared with the results from controls. Serum calcium levels were also measured and compared in both groups. Design- Case-control study.

RESULTS

Serum magnesium was found to be significantly low among cases with migraine compared to controls. Serum magnesium levels showed inverse correlation with frequency of migraine attacks, implying the role of a decreased serum magnesium level in defining the susceptibility to migraine. Results also showed an association between serum magnesium and calcium levels. Serum calcium was found to be low when serum magnesium was low.

CONCLUSION

Magnesium has a fundamental role in establishing the threshold for migraine headaches.

KEYWORDS

Migraine, Magnesium, Cortical, Excitability, Threshold.

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BACKGROUND

Migraine is the most common acute, recurrent headache syndrome.¹ The WHO has identified primary headaches including migraine as a major public health problem due to their high prevalence, widespread age and geographic distribution and their significant functional and socioeconomic impact.² The excitability of the cerebral cortex in the interictal state of migraine appears to be fundamental in the brain's susceptibility to migraine attacks.³ Cortical spreading depression has been suggested as the underlying mechanism of migraine aura.⁴ In the last few years, a fundamental role for magnesium (Mg^{2+}) in establishing the threshold for migraine attacks and involvement in the pathophysiologic mechanisms related to

its onset has become evident.⁵ Magnesium concentration has an effect on NMDA (N-Methyl D-Aspartate) receptors, nitric oxide synthesis and release, serotonin receptors and a variety of other migraine-related receptors and neurotransmitters.⁶ Changes in neuroexcitatory aminoacids and magnesium have shown to reflect a predisposition of the migraine patient notably those having attacks with aura to develop spreading depression.⁷ Magnesium deficiency has also been implicated in the phenomenon of central sensitisation leading to escalation of episodic migraine to chronic migraine.⁸ Measurement of serum magnesium is the most available and commonly employed test used to assess magnesium status.⁹

Magnesium appears to be a special kind of calcium channel antagonist in vascular smooth muscle.¹⁰ Headache has often been described in the hyperexcitability syndrome, which recognises an alteration of calcium (Ca^{2+}) and magnesium status in its aetiopathogenesis. In migraine patients, magnesium has been shown to play an important role as a regulator of neuronal excitability and therefore hypothetically of headache.¹¹

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AIMS AND OBJECTIVES

1. To find the relationship between serum magnesium level and physiologic threshold for migraine.
2. To find the association between serum magnesium and serum calcium levels in migraine patients.

MATERIALS AND METHODS

Study Design- Case-Control Study.

Sample Size- 70 cases and 70 Controls.

The study group comprised of 70 adults (29 males and 41 females) of age 18 to 40 years who attended Neurology Outpatient Clinic, Government Medical College, Thiruvananthapuram, clinically diagnosed with migraine by neurologist and classified into migraine with aura and migraine without aura according to the criteria set by the Headache Classification Committee of the International Headache Society (IHS II- 2004).¹² The patient group was divided into two subgroups- Migraine with aura (15 females and 5 males) and migraine patients without aura (26 females and 24 males) based on the criteria of IHS II 2004. Equal number of age and sex matched healthy volunteers with no history of headaches were enrolled as controls.

Inclusion Criteria

Adult males and females of age 18 to 40 years diagnosed with migraine who were in the interictal period were selected as cases.

Exclusion Criteria

Less than 72 hours after headache.
Prophylactic antimigraine therapy.
Diabetes mellitus.
Epilepsy and antiepileptic therapy.
History of cerebrovascular accident.

Screening of patients was done based on a proforma, which included history of headaches including frequency, disease duration and other medical illness. Menstrual and obstetric history was recorded in female patients. Estimation of serum magnesium and calcium were done in the Surgical Research Lab, Government Medical College, Thiruvananthapuram, after obtaining voluntary consent from all cases and controls.

The study was approved by the Institutional Research Committee and Human Ethics Committee, Government Medical College, Thiruvananthapuram.

Methodology

Under aseptic precautions, 3 mL of blood was taken in a plain glass bottle for estimation of serum magnesium and calcium. Serum magnesium was estimated by the Xylidyl Blue method using Wako Magnesium B test kit. Arsenazo 111 method was used for measurement of serum calcium.

Estimation of Serum Magnesium

Xylidyl Blue Method

Xylidyl Blue method is an invitro colorimetric method for the quantitative determination of magnesium in serum. This test allows measurement of magnesium in a one-step procedure without using any organic solvent. Ascorbic acid, bilirubin and haemolysis do not influence the assay of magnesium by this procedure.

Reagents and Materials

Colour	Xylylazoviolet-1(XB-1)	0.1 mmol/L
	GEDTA	0.045 mmol/L
	Surfactant	
Standard	Magnesium	5 mg/dL

1. Test tubes (washed with dilute hydrochloric acid or dilute nitric acid).
2. Micropipette 0.02 mL.
3. Pipette 3.0 mL.
4. Semi-auto biochemical analyser.

Expected values

Serum magnesium-1.9-2.5 mg/dL (1.56-2.05 mEq/L).

Estimation of Serum Calcium

Arsenazo 111 Method

Arsenazo 111 combines with calcium ions at pH 6.75 to form a coloured chromophore, the absorbance of which is measured at 650 nm (630-660 nm) and is proportional to calcium concentration. Arsenazo 111 has a high affinity for calcium ions and shows no interference from other ions normally present in serum, plasma or urine.

Reagent

Calcium Arsenazo Reagent

Arsenazo 111	0.20 mmol/L
Imidazole buffer (pH 6.75 ±0.1)	100 mmol/L

Expected values.

Serum calcium-8.4 to 10.4 mg/dL.

Statistical Analysis

Data were analysed using computer software SPSS version 10. Suitable statistical tools like Chi-square analysis, Student's t-test, one-way ANOVA with Duncan's multiple range test and linear regression analyses were performed to elucidate the results of the study. Analysis of variance (one-way ANOVA) was performed as parametric test to compare different variables between three groups, namely migraine without aura, migraine with aura and controls. For all statistical evaluations, probability of value <0.05 was considered significant.

RESULTS

Parameters	Group	Mean	± SD	t value	p value
Serum Mg ²⁺ (mEq/L)	Cases	1.60	0.30	-2.388	<0.05
	Control	1.72	0.30		
Serum Ca (mg %)	Cases	9.01	1.35	-2.047	<0.05
	Control	9.51	1.53		

Table 1. Comparison of Serum Magnesium and Serum Calcium Levels between Cases and Controls

Serum magnesium and calcium showed significant ($p < 0.05$) difference between cases and controls, even though the mean difference obtained was low.

Mean age of 27.84 and 27.67 of cases and controls respectively implied no significant difference in age group between cases and controls. There was a higher female representation in cases evident in sex ratio (0.71) of cases. No significant difference was found between males and females among cases with respect to mean serum magnesium and calcium levels. Significantly high incidence of menstrual migraine and premenstrual syndrome was found in the aura group than in the without aura group, among female migraineurs.

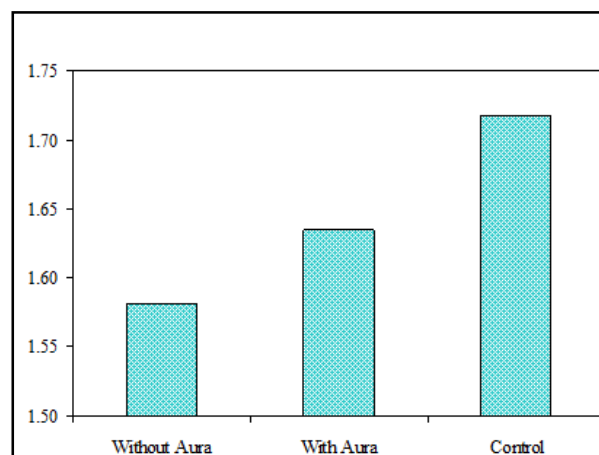


Figure 1. Mean Serum Magnesium (mEq/L) in Cases and Controls

Parameters	Category	Mean	± SD	F value	p value
Serum Mg ²⁺ (mEq/L)	Without aura	1.58 ^a	0.29	3.070	>0.05
	With aura	1.64 ^a	0.32		
	Control	1.72 ^a	0.30		
Serum Ca (mg%)	Without aura	8.97 ^a	1.41	2.160	>0.05
	With aura	9.12 ^a	1.23		
	Control	9.51 ^a	1.53		

Table 2. Comparison of Mean Serum Magnesium and Calcium in the Three Tested Groups (Analysis of Variance (ANOVA))

a -mean values with same superscript in each row do not differ each other (Duncan's multiple range test).

No significant ($p > 0.05$) difference was seen between migraine with aura and without aura groups of cases with respect to mean serum magnesium and serum calcium levels. However, the control group showed highest values of magnesium and calcium content in serum.

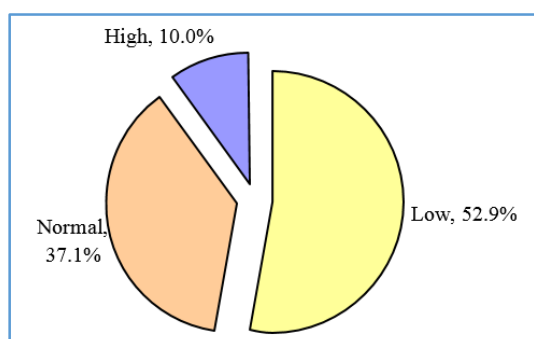


Figure 2. Distribution of Serum Magnesium Concentration among Cases

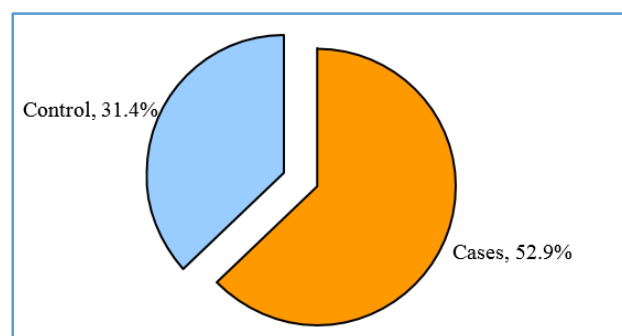


Figure 3. Percentage Distribution of Cases and Controls with Low Serum Magnesium

Correlation between multiple parameters among cases with migraine							
Parameters	Age	Gender	Serum Mg ²⁺	Serum Ca	Age at Onset	Duration in years	Last Attack
Serum Mg ²⁺	0.002	-0.07	1				
Serum Ca	0.020	-0.003	0.405**	1			
Age at Onset	0.133	0.114	-0.187**	-0.188*	1		
Duration in years	0.367**	0.228**	-0.09	-0.059	0.689**	1	
Last Attack	-0.054	0.016	-0.155	-0.123	0.812**	0.523**	1
Frequency	0.222**	0.223**	-0.201*	-0.125	0.680**	0.791**	0.463**

*p<0.05; ** p<0.001

Table 3. Correlation between Multiple Parameters among Cases with Migraine

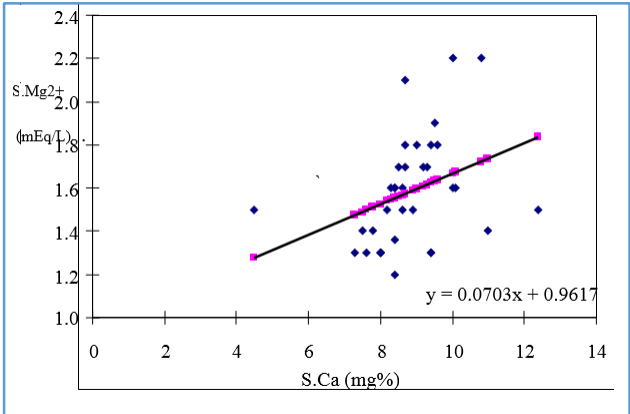


Figure 4. Relationship between Serum Magnesium and Serum Calcium Levels among Cases

Serum magnesium and calcium content in serum of cases showed a significant positive correlation and regression with a lower slope value. Serum calcium depicted a low value when magnesium level was low.

DISCUSSION

Results of this study point to an association between low serum magnesium levels and susceptibility to migraine headaches. Diagnosis of magnesium deficiency is usually made by a low-serum magnesium concentration and majority of our experimental information comes from determination of magnesium in serum and red blood cells.¹³In this study, serum magnesium was measured between attacks as the excitability of the cerebral cortex in the interictal state of migraine appears to be fundamental in the brain's susceptibility to migraine attacks. Results of this study showed significant (p<0.05) difference in mean serum magnesium levels between migraine cases and healthy controls, even though the mean difference obtained was low (Table 1). A prior evaluation by Thomas et al showed a mean serum magnesium level of 0.82

mmol/litre in migraine patients and 0.85 mmol/litre in controls with p<0.005. The same study also registered a mean erythrocyte magnesium level of 2.04 mmol/litre in migraine patients and 2.32 mmol/litre in controls, which was highly significant. It was concluded that migraine patients have a magnesium deficit as a frequent occurrence, although not a constant finding.⁵

In comparison with normal subjects, migraine patients have shown lower levels of serum and salivary magnesium interictally. Serum magnesium levels tended to be further reduced during attacks, which could be an expression at the peripheral level of reduced cerebral magnesium levels, which would contribute, at least in part, to defining the threshold for migraine attacks.¹⁴ Studies by Welch et al indicates that low intracellular brain magnesium concentration maybe the link between the physiologic threshold for migraine and the attack itself.¹⁵Sarchielli et al stated that serum magnesium levels might express indirectly the lowering of brain extracellular magnesium concentration, which occurs in migraine patients.⁶ Studies by Welch and Ramadan¹⁵ supported the presence of both systemic and brain magnesium deficiency in migraineurs particularly in the occipital lobes. Magnesium depletion by potentiating NMDA receptor stimulation produces an increase in activity of the excitatory system, thereby modulating the neuronal excitability in migraine.¹⁶It has been proposed that migraine sufferers have a susceptibility to spontaneous neuronal discharges and subsequent spreading depression, supported by increased turnover of high energy phosphates, low intracellular magnesium and large amplitude depolarising waves on magnetoencephalography.¹⁷ Some results suggest that the concentration of free ionised Mg²⁺ in the plasma maybe a better index of Mg²⁺ status than the total serum Mg²⁺ concentration, but further evaluation is necessary.¹⁸

Magnesium depletion seems to help release serotonin from its storage sites and also makes blood vessels in the brain more receptive to serotonin and thus clears the way for serotonin to cause constriction of blood vessels.¹⁹ A fall in magnesium concentration also allows a greater rise in intracellular calcium,²⁰ which activates Nitrous Oxide Synthase (NOS) causing release of nitric oxide.²¹ Nitric oxide mediates a variety of physiological phenomena like initiation of perivascular neurogenic inflammation with liberation of vasoactive peptides.²² The neuroinflammatory response to cortical spreading depression like extravasation of plasma proteins maybe in part due to up-regulation of inducible NOS.²³

Though statistically significant ($p < 0.05$) low values of serum magnesium was found in cases of migraine compared to controls on comparing among the three tested groups, no significant difference was observed individually (Table 2). Also, no statistically significant difference was revealed between the migraine with aura and without aura groups with respect to mean serum magnesium or calcium levels. This observation maybe accounted for by the lesser number of cases in the aura group of migraineurs enrolled in the study population. In the study, 52.9% of migraine cases showed low magnesium levels in serum, whereas only 31.4% had low serum magnesium in the control group (Figure 3). The study thus replicates the observations in previous studies and also point to the possible role of lowered serum magnesium level in defining the susceptibility to migraine. This was further strengthened by the observation that frequency of migraine attacks was related inversely to serum magnesium level, the frequency increasing when serum magnesium was low (Table 3). These observations provide evidence to the increase in susceptibility to migraine in individuals with low levels of serum magnesium and the hypothetical involvement of magnesium in the genesis of migraine.

In this study, menstrual migraine and Premenstrual Syndrome (PMS) showed significantly higher distribution ($p < 0.001$ and $p < 0.05$, respectively) in the aura group of female migraineurs. However, the association between this observation and serum magnesium levels in both groups of female patients could not be elucidated because of lower subgroup numbers. Relative dopamine deficiency has been implicated as a trigger for premenstrual migraine. Magnesium deficiency maybe directly involved in central nervous system dopamine deficiency as confirmed by studies in laboratory animals.²⁴ High levels of oestrogen and progesterone deplete, significantly, magnesium in cerebral vascular smooth muscle cells possibly resulting in cerebral vasospasms and reduced cerebral blood flows related to premenstrual syndromes.

Mauskop and Altura through their study supported the efficacy of magnesium on acute and prophylactic management of menstrual migraine, because of an excellent safety profile and low cost.²⁵ Study by Piekert et al also found high dose oral magnesium to be effective in migraine prophylaxis.²⁶ This study, not being a clinical trial

or followup study could not arrive upon similar conclusions; however, the significantly low ($p < 0.05$) mean value of serum magnesium in migraine cases compared to controls and the higher percentage distribution of cases with low serum magnesium underscores the possible significance of magnesium as a prophylactic agent in migraine. The observation that frequency of migraine attacks was related inversely to serum magnesium levels further strengthens this hypothesis.

Results of this study also revealed a significant relationship between serum magnesium and calcium, serum calcium level decreasing with a decrease in serum magnesium and vice versa. Magnesium has been called 'nature's physiological calcium channel blocker.' During Mg^{2+} depletion, intracellular Ca^{2+} rises. This may be caused by both uptake from extracellular Ca^{2+} and release from intracellular Ca^{2+} stores.²⁰ Hypocalcaemia is a common manifestation of moderate-to-severe Mg^{2+} depletion and maybe a major contributing factor to the increased neuromuscular excitability often present in Mg^{2+} depleted patients. Magnesium is required to maintain normal parathormone responses and impaired parathormone release along with diminished target organ response account for the hypocalcaemia that occurs in magnesium deficiency.²¹

CONCLUSION

Magnesium has a possible role in defining the susceptibility to migraine and a modulatory role in various mechanisms of migraine genesis. Although, various mechanisms have been suggested to explain the association between magnesium and physiologic threshold for migraine, more studies at cellular and molecular levels are needed to further elucidate this association. Magnesium, being a common denominator in most mechanisms of migraine genesis is a likely candidate molecule for prophylactic migraine therapy.

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REFERENCES

- [1] Swaiman KF, Ashwal S, Ferriero DM. Paediatric neurology: principles and practice. 4th edn. Vol. 2. Philadelphia: Elsevier 2007.
- [2] Jette N, Patten S, Williams J, et al. Comorbidity of migraine and psychiatric disorders--a national population-based study. *Headache* 2008;48(4):501-516.
- [3] Lang E, Kaltenhäuser M, Neundörfer B, et al. Hyperexcitability of the primary somatosensory cortex in migraine- a magnetoencephalographic study. *Brain* 2004;127(11):2459-2469.
- [4] Richter F, Lehmenkühler A. Cortical spreading depression (CSD): a neurophysiological correlate of migraine aura. *Schmerz* 2008;22(5):544-546, 548-550.

- [5] Thomas J, Tomb E, Thomas E, et al. Migraine treatment by oral magnesium intake and correction of the irritation of buccofacial and cervical muscles as a side effect of mandibular imbalance. *Magnes Res* 1994;7(2):123-127.
- [6] Sarchielli P, Coata G, Firenze, et al. Serum and salivary magnesium levels in migraine and tension type headache. Results in a group of adult patients. *Cephalalgia* 1992;12(1):21-27.
- [7] Ferrari MD. Biochemistry of migraine. *Pathol Biol* 1992;40(4):287-292.
- [8] Begon S, Pickering G, Eschaliel A, et al. Role of spinal NMDA receptors, protein kinase C and nitric oxide synthase in the hyperalgesia induced by magnesium deficiency in rats. *British Journal of Pharmacology* 2001;134(6):1227-1236.
- [9] Bennett GJ. Update on the neurophysiology of pain transmission and modulation: focus on the NMDA-receptor. *J Pain Symptom Manage* 2000;19(1 Suppl):S2-6.
- [10] Altura BM, Altura BT, Carella A, et al. Mg^{2+} - Ca^{2+} interaction in contractility of vascular smooth muscle: Mg^{2+} versus organic calcium channel blockers on myogenic tone and agonist-induced responsiveness of blood vessels. *Can J Physiol Pharmacol* 1987;65(4):729-745.
- [11] Mazzotta G, Sarchielli P, Alberti A, et al. Electromyographical ischemic test and intracellular and extracellular magnesium concentration in migraine and tension-type headache patients. *Headache* 1996;36(6):357-361.
- [12] International Headache Society Classification Subcommittee. The international classification of headache disorders. 2nd edn. *Cephalalgia* 2004;24(Suppl1):1-160.
- [13] Rude RK. Magnesium metabolism and deficiency. *Endocrinol Metab Clin North Am* 1993;22(2):377-395.
- [14] Gallai V, Sarchielli P, Coata G, et al. Serum and salivary magnesium levels in migraine. Results in a group of juvenile patients. *Headache* 1992;32(3):132-135.
- [15] Welch KM, Barkley GL, Tepley N, et al. Central neurogenic mechanisms of migraine. *Neurology* 1993;43(6 Suppl 3):S21-25.
- [16] Qian A, Buller AL, Johnson JW. NR2 subunit-dependence of NMDA receptor channel block by external Mg^{2+} . *Journal of Physiology J Physiol* 2005;562(Pt 2):319-31.
- [17] Welch KM, Barkley GL, Ramadan NM, et al. NMR spectroscopic and magnetoencephalographic studies in migraine with aura: support for the spreading depression hypothesis. *Pathol Biol (Paris)* 1992;40(4):349-354.
- [18] Altura BM, Altura BT. Role of magnesium in pathophysiological processes and the clinical utility of magnesium ion selective electrodes. *Scand J Clin Lab Invest Suppl* 1996;224:211-234.
- [19] Dean C. The clinical impact of magnesium deficiency. 74th congress. 2nd session.
- [20] Stipanuk MH. Biochemical, physiological and molecular aspects of human nutrition. 2nd edn. Elsevier 2006.
- [21] Ganong WF. Review of medical physiology. 21st edn. McGraw Hill 2003.
- [22] Thomsen LL, Olesen J. Nitric oxide theory of migraine. *Clin Neurosci* 1998;5(1):28-33.
- [23] Bradley WG, Daroff RB, Fenichel GM, et al. The neurological diseases. *Neurology in clinical practice*. 5th edn. Vol. 2. Philadelphia: ButterworthHeinman Elsevier 2008.
- [24] Barbeau A, Rojo-Oretega JM, Brecht HM, et al. Deficiency in magnesium et dopamine cerebrale. In: Durlach J, ed. First international symposium on magnesium deficit in human pathology. Vittel, Paris: 1973.
- [25] Mauskop A, Altura BT, Altura BM. Serum ionized magnesium levels and serum ionized calcium/magnesium ratios in women with menstrual migraine. *Headache* 2002;42(4):242-248.
- [26] Peikert A, Wilimzig C, Kohne-Volland R. Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study. *Cephalalgia* 1996;16(4):257-263.