

# Magnesium ion serum profile in chronic migraine: comparative study between treated and non-treated patients

Perfil sérico do íon magnésio na migrânea crônica: um estudo comparativo entre pacientes tratados e não tratados

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## ABSTRACT

Chronic migraine is recognized as a migraine complication and is characterized by frequency of attacks up to 15 days/month for more than three months, in absence of painkiller abusive usage. Studies indicate that magnesium ion plays a role in migraine pathophysiology but, until now, they have never included only patients with chronic migraine as their population. **Objective:** To compare serum magnesium levels between treated and non-treated chronic migraineurs. **Methods:** Twenty-two patients with chronic migraine were selected and divided in two groups (treated and non-treated), matched by sex and age, and submitted to serum dosage of magnesium ion for latter comparison. **Result:** The non-treated chronic migraineurs presented serum magnesium ion level within normal limits, but lower than those found in the treated group with a statistically significant difference. **Conclusion:** Similarly to other studies in the literature, this study stresses the importance of magnesium ion in the migraine pathophysiology, but studying only the chronic migraine patients.

**Keywords:** Chronic migraine; Serum magnesium; Pathophysiology

## RESUMO

Migrânea crônica refere-se a uma complicação da migrânea e é caracterizada por uma frequência de crises superior a 15 dias por mês durante mais de três meses, sem uso excessivo de analgésicos. Pesquisas demonstram que o íon magnésio está envolvido na fisiopatologia da migrânea, contudo nunca incluíram, até o momento, pacientes com migrânea crônica como população exclusiva. **Objetivo:** Comparar os níveis de magnésio sérico entre migranosos crônicos tratados e não tratados. **Métodos:** Vinte e dois pacientes com migrânea crônica foram selecionados; divididos em dois grupos (tratados e não tratados); pareados por sexo e idade e submetidos à dosagem sérica do íon magnésio para comparação posterior dos resultados obtidos. **Resultado:** Os migranosos crônicos não tratados apresentaram níveis de magnésio sérico dentro dos limites da normalidade, embora menores que os

encontrados no grupo tratado, com uma diferença estatisticamente significativa. **Conclusão:** Em corroboração com a literatura, este estudo enfatiza a importância do íon magnésio na fisiopatologia da migrânea, apenas pacientes com migrânea crônica.

**Palavras-chave:** Migrânea crônica; Magnésio sérico; Fisiopatologia

## INTRODUCTION

As a common and disabling disorder, migraine is the most studied primary headache nowadays.<sup>(1)</sup> Studies reveal a prevalence of 11% of migraine in the general population,<sup>(1)</sup> and 38% of headache patients admitted in a tertiary center.<sup>(2)</sup> According to the World Health Organization ranking, migraine holds the 19th position among all the disabling diseases.<sup>(1)</sup> Chronic migraine is considered by the International Classification of Headache Disorders, 2<sup>nd</sup> edition (ICHD-2), as a migraine complication, whose main characteristics are: frequency of migraine attacks up to 15 days/month for more than three months, in absence of painkiller abusive usage.<sup>(3)</sup>

Considering the pathophysiology of migraine, magnesium ion is referred as a possible biomarker.<sup>(4-7)</sup> This ion has been already described as deficient at systemic and brain levels in patients with migraine (with and without aura) and in those with menstrual migraine.<sup>(6,7)</sup> Moreover, studies show that in long-duration attacks the trigeminal system is sensitized, what happens due to continuous and repetitive stimulation of the primary afferent neuron through long term glutamate release and  $Mg^{2+}$  depletion from NMDA receptors, followed by glutamate binding to these receptors.<sup>(6)</sup> Thus, it leads to calcium influx in neurons of the trigeminal nucleus caudalis, its sensitization and increase of cortical excitability.<sup>(4-6)</sup> In addition to these evidences, measures of magnesium ion obtained through phosphorus-31 spectroscopy revealed low levels in the brain posterior areas of people with familial hemiplegic migraine.<sup>(6,8)</sup>

The above-mentioned mechanism induces not only epileptiform discharges and cortical spreading depression, but also arterial vasospasm due to low serotonin (5-HT) levels and other vasoactive substances.<sup>(9)</sup> More than that, it increases thrombin-induced platelet aggregation, leading to 5-HT release, reduction on prostacyclins action over  $\beta$ -adrenergic-mediated relaxation of the blood vessel walls. Consequently, low magnesium levels act as a pro-inflammatory agent.<sup>(9)</sup>

The entire amount of magnesium in an adult human is about 24 g (1 mol) and it is equally distributed among bones and soft tissues.<sup>(10)</sup> Less than 1% of total body magnesium is contained in the blood and approximately 0.3%, presented in serum.<sup>(10)</sup> Serum magnesium measurement has been largely used to estimate the amount of this ion in the organism.<sup>(10)</sup> Therefore, researches have already been made comparing magnesium levels between patients with headache and healthy volunteers,<sup>(11)</sup> in accord to dosage of magnesium ion in migraineurs with and without aura in the interictal period,<sup>(12,13)</sup> in patients with menstrual migraine<sup>(14)</sup> and in others with hemodialysis headache.<sup>(15)</sup>

However, there are no citations of the serum levels of magnesium in patients with chronic migraine. This study tries to elucidate how magnesium ion acts in chronic migraine, by comparing serum magnesium levels between treated and non-treated chronic migraineurs, it also analyzes clinical characteristics of these patients.

## METHODS

The study was performed on patients of the headache center of the Liga de Cefaleia de Sergipe, located at the Teaching Hospital of the Universidade Federal de Sergipe. A total of 22 patients, diagnosed with chronic migraine by the same examiner according to criteria of the ICHD-2, were divided in two groups. The Group A was composed by eleven patients without any kind of behavioral intervention or previous drug therapy, at the moment of first admission; the 11 remaining patients, who were arranged into the Group B, that had already been under treatment in that center and achieved a reduction of their frequency of attacks for less than 15 days per month, as assured by migraine-daily chart. None of these patients were using any medication containing magnesium for headache therapy or any other purpose.

A dosage of serum magnesium ion was requested for all the 22 patients at one laboratory in the city of Aracaju, capital of Sergipe. This laboratory, whose serum magnesium ion reference values range 1.6 to 2.3 mg/dL, was not informed about the reason for requesting such exam. Then, the results of each group were compared through Student's t-test.

This research was approved by the Ethics Committee of the Teaching Hospital of the Universidade Federal de Sergipe and all participants included have signed a permission term according to Helsinki Declaration rules.

## RESULTS

In both groups, most members were women, being nine for group A and ten for group B. The average age in group A was  $43 \pm 14.9$  years old, whereas in group B, it was  $41.0 \pm 14.6$  years old. Considering the age of onset of migraine attacks, it varied from 6 to 48 years for group A, and from 3 to 44 years for group B. The period of chronification, 48 months, was similar in both groups. The majority of subjects presented serum magnesium levels within normal limits; except for one patient in group A whose ion level was below 1.6 mg/dL, and another in group B who showed magnesium level above 2.3 mg/dL (Table).

Table - Relationship between the variables age, age of migraine onset (AMO, years), time of chronification (TC, months) and serum levels of magnesium (reference value of the laboratory: 1.6 to 2.3 mg/dL) in relation to the groups A and B

	Group	n	Mean	Std. Dev.	t-test	P
Age	A	11	43.27	14.88	0.332	0.743
	B	11	41.18	14.65		
AMO	A	11	20.64	12.37	1.139	0.268
	B	11	14.64	12.33		
TC	A	11	48.00	50.63	-0.009	0.993
	B	11	48.18	47.88		
Mg <sup>2+</sup>	A	11	1.72	0.15	-3.895	0.001
	B	11	2.02	0.21		

Even though results of the samples were normal in 20 of the 22 patients undergoing research, when Student's t-test was applied in order to compare magnesium levels of both groups, it was demonstrated that serum magnesium levels of group A were lower than group B, with a statistically significant difference ( $p=0.001$ ).

## DISCUSSION

It is reckoned that chronic migraine is a complication of episodic migraine.<sup>(3)</sup> Some risk factors are believed to be related to the transformation, such as caffeine, painkiller abusive consumption, obesity, psychiatric comorbidities, Caucasian race, sleep disturbances, lower socioeconomic status, among others.<sup>(16-18)</sup> Also, female gender is considered a risk factor for chronification of migraine.<sup>(16,17)</sup> Twenty-two patients took part in this study; among them, there has been observed female predominance ( $n=19$ ), oppositely to male gender ( $n=3$ ). Chronic migraine is more prevalent during childbearing age (15-49 years)<sup>(16)</sup> in the female gender and during adulthood among the male group (25-49 years).<sup>(18)</sup> Corroborating with these

data, the sample of the present study was composed of 19 women, whose mean age was 46 years in the group A and 41.8 in group B. Similarly, the average age for men was compatible with the literature.

In this study, the age of onset of migraine varied from 3 to 48 years old, with mean age of  $17.6 \pm 12.5$  years, similar to the reviewed literature (mean age:  $20.8 \pm 11.2$  years).<sup>(19)</sup> Considering time of chronification, our patients presented, in mean, a period of 48 months, a result that does not corroborate with some studies in the literature which demonstrate a mean period of 12 months of transformation from episodic to chronic migraine.<sup>(16,17)</sup>

Several studies correlate changes on serum magnesium levels with threshold and continuance of pain attacks, reinforcing the importance of this ion in the pathophysiology of various types of headache. Gallai et al.,<sup>(13)</sup> when comparing magnesium levels in the blood of patients suffering from migraine with aura, without aura and controls, observed a lower concentration of intracellular magnesium in migraineurs than in the control group.

Mauskop et al.,<sup>(14)</sup> while studying the level of free magnesium ion on 61 women with menstrual migraine and patients without headache, found low magnesium ion levels in 45% of women with menstrual migraine, whereas only 14% of the menstruant women without migraine had low free magnesium levels. All women had normal total magnesium, and the researchers did not find a correlation between the level of free magnesium and the intensity of chronic headache.

Furthermore, Goksel et al.<sup>(15)</sup> studied serum levels of magnesium before and after hemodialysis on patients with dialysis headache compared to a control group of people suffering from chronic kidney disease. There have been found, on patients with dialysis headache, lower levels than in the control group before and after hemodialysis, but the absolute level of magnesium was normal in both groups (reference levels: 1.6-3.0 mg/dL).

Once magnesium-deficient state has been recognized, the supplementation of this ion was suggested as a possible therapy for patients with headache, as much for abortive, as for prophylactic treatment.<sup>(9,20)</sup> A study with 81 migraineurs in use of 600 mg of magnesium dicitrat in the form of a soluble powder in water and placebo has shown a 42% decrease in the frequency of crisis with such medication, while those that received placebo presented decreasing of headache attacks only on 16% after 12 weeks.<sup>(9)</sup> Another study conducted by Mauskop et al.<sup>(20)</sup> revealed that intravenous magnesium aborted migraine

attacks of high intensity on patients with low magnesium serum levels, but not on patients with normal ones.

## CONCLUSIONS

Until now, there is no study in the literature which correlates exclusively chronic migraine and serum magnesium ion levels. In this research, non-treated patients with chronic migraine presented normal serum magnesium levels, but significantly lower when compared to patients that, under treatment, would be then classified as episodic migraineurs. This study was carried out with a reduced number of patients, which limits a more precise conclusion. However, like other studies, it points magnesium ion as a possible biomarker of pathophysiological mechanisms of migraine.

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## COMMENTS

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Jesus and colleagues show, concisely, in article “Magnesium ion serum profile in chronic migraine: comparative study between treated and non-treated patients” that magnesium ion plays a role in pathophysiology of migraine. According to these authors, serum magnesium levels are reduced in patients with migraine. This change would make it a migraine biomarker. This information can also be seen in research Talebi et al.<sup>1</sup>

As result of magnesium deficiency, Jesus and colleagues cite the supplementation of this ion in both abortive and prophylactic treatment of migraine. However, in a recent review on the acute treatment of migraine,

Kelley et al.<sup>2</sup> found that magnesium seems to have only limited effectiveness in treating photophobia and phonophobia.

As demonstrated, current research on the role of magnesium in pathophysiology and treatment of migraine have been performed only in episodic migraine. This article is certainly the first on the magnesium ion in patients with chronic migraine.

Finally, the findings of lower serum magnesium levels in patients with untreated chronic migraine corroborate the fact that repeated attacks of headache causes continuous stimulation of primary afferent neuron, with consequent depletion of magnesium.

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