

Serum ionized magnesium and calcium level in adult migraineurs during interictal period in comparison with control group

Seyyed Ali Roodbari¹, Ali-Asghar Abrishamizadeh¹

Iranian Journal of Neurology, Vol.7, No.23, Autumn 2008, 230-238

Introduction: Nowadays, many studies consider a role for magnesium and calcium in pathophysiology and treatment of migraine. We evaluated serum ionized magnesium and calcium level in migraineurs -during interictal period- and control group.

Methods: Migraineurs -according to the IHS criteria- enrolled in this study. Serum Mg²⁺ and Ca²⁺ level were determined by atomic absorption spectrophotometry. Mean values were compared, using t-test.

Results: 40 migraineurs and 40 healthy subjects (34 (85%) female and 6 (15%) male in each group) enrolled the study with mean age of 34.8±9.9 and 35.7±9.1 years, respectively. There were no significant difference between Mg²⁺ levels in cases vs. healthy subjects (1.55±0.27 vs. 1.55±0.29 meq/l) but serum Ca²⁺ level was lower in healthy subjects. (8.04±1.18 vs. 7.56±0.82 meq/l, P<0.05).

Migraineurs without aura had lower serum Mg²⁺ level (1.56±0.26 vs. 1.76±0.24 meq/l) and higher serum Ca²⁺ level (8.10±1.23 vs. 7.64±0.65 meq/l) than with aura migraineurs. Migraineurs with "monthly attack rate ≥4" had lower Mg²⁺ and Ca²⁺ level (1.48±0.23 vs. 1.58±0.29 meq/l) and (7.95±0.42 vs. 8.09±1.85 meq/l) than those with lower attack rate. Females whose attacks aggravated by menstruation had lower serum Mg²⁺ and Ca²⁺ level in comparison with those their attacks didn't aggravate by menstruation (1.46±0.25 vs. 1.77±0.25 and 7.77±0.59 vs. 8.80±2.77, P<0.05).

Conclusion: In our study, severity of migraine had correlation with reduced serum Mg²⁺ and higher Ca²⁺ level which confirms the role of reduced magnesium level on lowering the threshold of attacks. Also, lower Mg²⁺ and higher Ca²⁺ level in migraineurs without aura could exhibit a demonstrable calcium channelopathy, but also raises questions about possibility of different mechanisms for "with and without aura" migraine. However, it seems that further studies with larger sample size and intra cellular (RBC and monocyte) Mg²⁺ assessment, is needed.

Keywords: Headache, Migraine, Magnesium, Calcium

¹ Neurologist

Introduction

Headache is a prevalent complaint among clinics clients.⁽¹⁾ It strikes 1 out of each 3 persons all over the world in at least one stage of life.⁽²⁾ Approximately, 90% of cases with recurrent headaches are primary in etiology like Migraine, tension and cluster headaches.⁽³⁾ Among them common migraine is the most prevalent one.⁽⁴⁾ In America migraine prevalence is 6% in males and 17.6% in females.⁽³⁾ Migraine is a chronic disease by episodic attacks that also induces levels of disability during attacks intervals.⁽³⁾ In the U.S reduction of worker productivity for headache is about 6.5-17.2 billions dollars annually, in comparison to 2.6 for diabetes.⁽⁵⁾

Despite the importance and prevalence of migraine, unfortunately our knowledge is limited about it and in spite of the marked progression on pathophysiology and pharmacology of migraine, which have been made during recent 15 years, its mechanism is still unknown⁽³⁾ and different theories has been given about it's pathogenesis, genetics and neurotransmitters, involved in it, that some are the base of the new treatments. Some have categorized headache in hyper-excitability syndrome and have considered a role for the variable calcium and magnesium body level in its etiology.⁽⁵⁾

During recent years, some investigators, has attached a great importance to the role of magnesium in pathophysiology

and treatment of migraine. Among different investigations on Mg²⁺ and migraine pathogenesis, there are different results. Some has detected decreased level of serum and RBC Mg²⁺ level during attacks intervals⁽⁶⁾ and some in migraine attacks.⁽⁷⁾ While in other studies there were no significant differences in platelet ionized magnesium level⁽⁸⁾ and also serum Mg²⁺ level⁽⁹⁾ among migraineurs and control group. Despite other studies, in the latter study, it's being concluded that Mg²⁺ level decrement dose not have any role on Migraine pathophysiology.⁽⁹⁾

These discrepancies and disagreement continues to magnesium therapeutic role in migraineurs. Some believe on its positive therapeutic role in acute attacks⁽⁷⁾ and also during attacks intervals^(10,11) and some investigators are suspicious to its preventive role.⁽¹²⁾

In this study we compared serum magnesium and calcium level in migraineurs, during interictal period and in control group.

Methods

Patients referred to Rasht neurologic clinics and Poorsina Hospital, were interviewed and those with migraine diagnosis according to the International Headache Society (IHS) criteria 40 migraineurs and 40 healthy subjects after matching with inclusion and exclusion criteria included in the study. (Table 1)

Table 1- serum Mg and Ca level in terms of different class of samples

	Migraine group									
	Family history		Duration of migraine (month)		Aggravation with menstruation		Monthly attack rate		Type of migraine	
	-	+	<84	>=84	-	+	<4	>=4	WA	WOA
serum Mg ²⁺	1.50	1.56	1.59	1.49	1.77*	1.46*	1.58	1.48	1.76	1.56
	±	±	±	±	±	±	±	±	±	±
	0.26	0.27	0.24	0.29	0.25	0.25	0.29	0.23	0.24	0.26
serum Ca ²⁺	7.87	8.07	8.27	7.84	8.80	7.77	8.09	7.95	7.64	8.10
	±	±	±	±	±	±	±	±	±	±
	0.58	1.47	1.74	0.68	2.77	0.59	1.84	0.42	0.65	1.23

Data presented as "mean±SD"

MOA=migraine without aura and MA=migraine with aura

*(P=0/01)

A questionnaire was filled for both groups by interview and also primary

Inclusion Criteria

- 1-Confirmation of migraine diagnosis by IHS criteria
- 2- Age between 18-65 years old
- 3- The initial age for migraine was less than 50 years old
- 4- At least one week had been past since the last headache attack
- 5- At least three months was passed from preventive drug usage as; β -Blockers, Ca²⁺ Channel Blockers, valporate and so on.
- 6- They signed the written informed consent.

Exclusion Criteria

- 1- Diabetes

neurologic and physical examination were done for them.

2- HTN

3- Renal failure and creatinine level more than 1.5 mg/dL

4-Hypo or hyper natremia

5- Hypo or hyper calcemia

6- Hypo or hyper kalemia

7- All the situations which would decrease Magnesium level:

- Decrease in intestinal absorption because of malnutrition, malabsorption, (chronic) vomiting or diarrhea, nasogastric aspiration.
- Drugs which would decrease magnesium level by increasing its renal excretion as: ethanol, cyclosporine, cisplatin, aminoglycosides, amphotericin B, capreomycin, diuretics, furosemide,

ethacrynic acid, acetazolamide, thiazides and chlorothalidone.

- Hyperthyroidism, hypothyroidism
- 8- Any situation which would increase magnesium level:
- Magnesium containing laxatives and antacids
 - Recent IV Magnesium therapy as in preeclampsia
- 9- Serum Protein or Albumin decreased level

All migraineurs were studied during their post-ictal phase and at least 7 days after their last attack. They were not under any preventive therapeutic regimen for 3 month. We also selected 40 healthy as the control group.

Venous blood sample were drawn from the antecubital vein using a disposable injector into silicon-coated plastic tubes with EDTA-K and centrifuged at 3000 rpm for 10 minutes. In order to avoid the effect of circadian variations, venous blood samples were collected between 8 a.m. and 10 a.m. after an overnight fast. Samples were stored at -20°C. Serum Mg²⁺ and Ca⁺ level were determined using atomic absorption method and reported as meq/L.

Fasting blood sugar (FBS), total calcium level, creatinine, blood urea nitrogen (BUN), total protein level, serum albumin, sodium and potassium, urine specific gravity, complete blood count,

10- Chronic Alcohol use or Alcohol withdrawal

11- Parotidectomy or Thyroidectomy

12- Massive blood transfusion

13- Abnormal Neurologic Examination

14- ESR > 50 in a person older than 50 years old.

15- During the third trimester of pregnancy

16- Active and massive lactation

hematocrit and alkaline phosphatase were tested to rule out any other diseases.

Serum Mg²⁺ and Ca⁺ level were compared by independent-samples t-test using SPSS 10 software, for statistical evaluation. Data will be presented as number (frequency) or mean ± Standard deviation (SD).

Results

40 migraineurs (34 female and 6 male, with mean age of 34.88±9.97 years) entered the study according to 1998 IHS criteria. 40 age and sex matched healthy subjects (34 female and 6 male, with mean age of 35.7±9.1 years), was selected through volunteers without migraine and no chronic headache history. All subjects signed the written informed consent. Age distribution of two groups is presented in **Error!**
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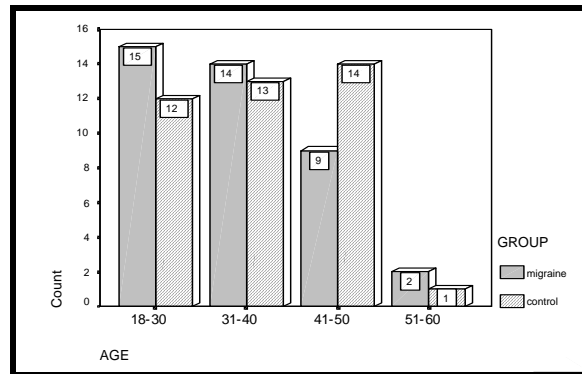


Figure 1: Comparing migraineurs and healthy subjects according to their age

Among migraineurs 24 (60%) had positive family history, 9 (22.5%) with negative family history and remaining couldn't give any information. Migraine attacks in 28 cases (82.35%) of woman were exacerbated by their menstruation. 5 patients (12.5%) had "migraine with aura" and 35 cases (87.5%) had "migraine without aura". Among the first group, 3 cases (60%) were female and 2 cases (40%) were male, and in the second group 31 cases (88.58%) were female and 4 cases (11.42%) were male.

All laboratory tests were normal in both groups.

Serum Mg²⁺ level was 1.55±0.27 meq/l (CI95%: 1.46-1.63) in migraineurs and 1.55±0.29 meq/l (CI95%: 1.45-1.64) in healthy subjects. Serum Ca²⁺ level was 8.04±1.18 meq/l (CI95%: 7.66-8.42) in migraineurs and 7.56±0.82 meq/l (CI95%: 7.30-7.82) in healthy subjects (P<0.05). Figure 2 shows serum Mg²⁺ and Ca²⁺ level in migraineurs and healthy subjects.



Figure2: serum Mg²⁺ level (left) serum Ca²⁺ level (right) in migraineurs and healthy subjects. (mean ± CI95%)

Women whose attacks aggravated by menstruation had lower serum Mg²⁺ level in comparison with those their attacks did not aggravate by menstruation (1.46±0.25 vs. 1.77±0.25 P<0.05).

Serum magnesium was lower in patients with positive family history of migraine, more than 84 month history of having migraine, having 4 or more attacks per month and migraine without

Discussion

Our study shows lower magnesium level in migraineurs compared with control group especially in subjects of migraine without aura and women with menstrually aggravated migraine compared with women whose attacks weren't aggravated with menstruation and control group (P<0/01) calcium 2+ level was high in patients with migraine without aura and patients with positive family history of migraine but in other migraineurs these finding wasn't seen except in patients with more than 4 attacks per month or more than 7 years history of migraine was higher Ca level.

According to various studies there are discrepancies and disagreements in results among different investigations on Mg²⁺ and migraine pathogenesis. Some has detected decreased levels of serum and RBC Mg²⁺ level during attacks' intervals⁽⁶⁾ and some in migraine attacks.⁽⁷⁾ While in other studies there were no significant differences in serum Mg²⁺ level⁽⁹⁾ among migraineurs and control group. Soriani et al.⁽²⁾ studied 25 male and 19

female migraineurs and found a significant decrease of serum and RBC Mg²⁺ level in this group in comparison to control group. In Galai et al. studies,^(5,6,13) lower serum Mg²⁺ level in interictal period among migraineurs vs. control group was detected.

In another study which was performed on 30 migraineurs and 19 tension headache patients,⁽⁴⁾ there was no significant difference in extracellular Mg²⁺ level between these two groups, intra RBC Mg²⁺ level was significantly lower in migraineurs. Schoenen J. et al.⁽⁷⁾ determined the same results, too. They determined significant lower Mg²⁺ level in migraineurs than control group. Smeets MC. et al.⁽¹⁴⁾ didn't find any difference between five groups' serum and RBC Mg²⁺ level; familial hemiplegic migraineurs (38 cases), healthy subjects in their family (11 cases), with aura migraineurs (9 cases), without aura migraineurs (23 cases) and control group (32 cases). They denied any association between Mg²⁺ level and migraine pathophysiology.

Sarchielli and Gallai⁽¹³⁾ detected a similar difference between with and without aura migraineurs. This would be because of the different pathophysiology for these two types of migraines.

In Facchinetti F. et al. study⁽⁸⁾ by oral magnesium treatment of patients with menstrual migraine attack, although monocyte Mg²⁺ level has been increased, it had not any influence on its serum level. Anyway attacks rate was lowered, so monocyte and intracellular Mg²⁺ level is more effective.

All of these results show the role of decreased Mg²⁺ level in lowering migraine attacks threshold. Also, the lower levels in without aura migraineurs arouse this question: "Would two different pathophysiologies for these two types of migraines be possible?"

Some studies consider a role for Ca²⁺ channel dysfunction^(15,16) as the basis for some neurological and muscle disorders such as migraine. Also there is some clue that hemiplegic migraine can be due to mutations in plasma-membrane Ca²⁺ channels.⁽¹⁷⁾

There is some evidence that Flunarizine, a class IV Ca²⁺ antagonist non-selective for slow Ca²⁺ channels, has beneficial effect in the prophylactic treatment of migraine.⁽¹⁸⁾

in maushop A and et al. study in 61 women with predominantly menstrual migraine measured Mg²⁺, Ca²⁺ and Ca²⁺ /Mg²⁺ ratio, the incidence of

Mg²⁺ deficiency was %45 during menstrual migraine, %15 during non menstrual attack, 14% during menstruation without migraine, %15 between menstruation and migraine attack his and Ca²⁺/Mg²⁺ ratio was elevated in menstrual migraine that reveals high incidence of Mg²⁺ deficiency and elevated Ca²⁺/Mg²⁺ ratio during menstrual migraine possibly due to Mg deficiency role in menstrual migraine in koseglu E et al. study in Turkey migraine attack frequency, seventy and P1/amplitude in VEP decrease after magnesium supplementation, in migraine without aura respect to pretreatment value (P<0/001).

In Silberstein and Goldberg study magnesium supplementation plays a role in preventing menstrually related migraine.

Conclusion

Our study results show that serum Mg²⁺ level in migraineurs' interictal period is lower than healthy subjects. Also serum Mg²⁺ and Ca²⁺ level correlates with the severity of migraine (monthly attack rate), chronicity and migraine without aura.

However it seems insufficient sample size is the major cause of making these differences statistically not significant and probably by studies with larger sample size and also measuring intracellular (intra RBC and monocyte) Mg²⁺ level, we can overcome this problem.

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مقایسه سطح سرمی منیزیوم و کلسیم یونیزه در افراد بالغ مبتلا به میگرن در سردرد بدون درد با افراد سالم

دکتر سید علی رودباری، دکتر علی اصغر ابریشم زاده

فصلنامه علوم مغز و اعصاب ایران، سال هفتم، شماره ۲۳، پاییز ۱۳۸۷، ۲۳۰-۲۳۸

چکیده:

زمینه و هدف: امروزه بسیاری از مطالعات نقشی برای منیزیوم و کلسیم در پاتوفیزیولوژی میگرن قائل شده‌اند. ما سطوح سرمی منیزیوم و کلسیم در دوره سردرد در افراد میگرنی و افراد سالم را در این مطالعه بررسی کردیم. روش بررسی: افراد مبتلا به میگرن بر طبق معیار I.H.S وارد مطالعه شدند. سطح سرمی Ca, Mg توسط روش جذب اتمیک با اسپکروفتومتر اندازه گیری شدند و میزان متوسط آنها با هم مقایسه و توسط روش t test آنالیز شد.

یافته‌ها: ۴۰ بیمار مبتلا به میگرن و ۴۰ فرد سالم شامل ۳۴ زن (۸۵٪) و ۶ مرد (۱۵٪) در هر گروه با متوسط سنی $34 \pm 9/9$ و $35/7 \pm 9/1$ سال به ترتیب وارد مطالعه شدند. هیچگونه تفاوتی بین سطح Mg^{2+} در افراد مبتلا به میگرن با افراد سالم وجود نداشت. $1/55 \pm 0/27$ در برابر $1/55 \pm 0/29$ meq / lit اما سطح سرمی کلسیم در گروه سالم نسبت به افراد مبتلا به میگرن پایین تر بود ($7/56 \pm 0/82$ Meq / lit) و $P < 0/5,5$ در برابر $(8/04 \pm 18/1)$

افراد میگرنی بدون اورا سطح سرمی منیزیوم پایین تری ($1/56 \pm 0/26$ در برابر $1/76 \pm 0/24$) و سطح سرمی کلسیم بالاتری ($1/23 \pm 8/10$ در برابر $7/64 \pm 0/56$) در مقایسه با افراد میگرن با او را داشتند. میگرنی‌ها با بیش از ۴ حمله در ماه نیز سطح سرمی منیزیوم پایین تر ($1/48 \pm 0/23$ meq / lit) در برابر $1/58 \pm 0/29$) و کلسیم پایین تری ($7/95 \pm 0/42$ meq / lit) در برابر $8/09 \pm 1/85$) نسبت به افراد با تعداد کمتر حملات سردرد در ماه داشتند. خانم‌هایی که حملات آنها با پیروید تشدید می شد سطح سرمی منیزیوم و کلسیم پایین تری در مقایسه با آنهایی که حملات سردرد شان ارتباطی با پیروید نداشت، داشتند. ($1/46 \pm 0/25$ /lit) در برابر $1/77 \pm 0/25$ و $7/77 \pm 0/59$ در برابر $8/88 \pm 2/77$ و $P < 0/05$)

نتیجه گیری: در مطالعه ما حملات میگرنی با کاهش سطح سرمی منیزیوم و افزایش سطح سرمی کلسیم داشت که نقش کاهش سطح منیزیوم در کاهش آستانه حملات میگرن و احتمال دخالت کانالوپاتی کلسیم و بروز تظاهراتی میگرن است و نیز می تواند بیانگر این مسئله باشد که میگرن با وبدون اورا ممکن است دو مکانیسم متفاوت داشته باشد.

به هر حال به نظر میرسد که مطالعات دیگری با حجم نمونه بیشتر و نیز بررسی سطح منیزیوم داخل گلوبولی منوسیت جهت ارزیابی نقش Ca, Mg نیاز باشد.

واژگان کلیدی: سردرد - میگرن - منیزیوم - کلسیم