Deficiency In Serum Ionized Magnesium But Not Total Magnesium In Patients With Migraines. Possible Role Of ICa^{2+}/IMg^{2+} Ratio

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SYNOPSIS

It has been suggested that magnesium (Mg) may play a role in the pathogenesis of headaches. Serum and intracellular measurements of Mg in headache patients have produced inconsistent results. The recent development of an ion-selective electrode for Mg^{2+} allowed precise measurement of serum ionized magnesium (IMg^{2+}) in patients with various headache syndromes. Low serum IMg^{2+} and a high ICa^{2+}/IMg^{2+} ratio were found in 42% of patients having an attack of migraine, but only in 23% of patients with e severe continuous headache. Total serum Mg was normal in both groups of patients. However, in patients with low serum IMg^{2+} total serum Mg was lower than in patients with normal serum IMg^{2+}. These results are compatible with the serotonin and vascular concepts of migraine pathogenesis. Low IMg^{2+} and a high ICa^{2+}/ IMg^{2+} would result in cerebral vasospasm and reduced blood flow in the brain. The activity of serotonin receptors can also be affected by changes in IMg^{2+} levels. The finding of a difference in IMg^{2+} levels in two different headache types suggests a possible novel classification of headaches and that migraine patients with a low serum IMg^{2+} or a high ICa^{2+}/IMg^{2+} ratio may benefit from Mg supplementation.

Key words: Magnesium, calcium, headache, migraine, pathogenesis, classification.

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INTRODUCTION

Due to lack of any objective measure the current International Headache Society (IHS) classification of headaches[1] is purely descriptive. A significant proportion of patients cannot be classified by this classification.[2] Diagnostic categories usually do not predict the efficacy of a certain treatment. For example, both migraines and chronic tension headaches may respond to tricyclic anti-depressants, while an acute severe headache of any type may respond to dihydroergotamine. Magnesium (Mg) may be one of the biological markers that can be used to classify headache types and, possibly, treat some of the patients.

Magnesium has long been implicated in the pathogenesis of headaches.[3-7] Several anecdotal reports[3-5] and one double-blind, placebo controlled trial[8] showed therapeutic efficacy of Mg supple-mentation in headache patients. One study found total serum Mg levels to be decreased in migraine and tension-type headache patients during an attack more than in the interictal period.[9] Two other studies showed normal serum levels of total Mg between attacks of migraine.[8,10] One of these studies demonstrated decreased total Mg concentration in erythrocytes,[10] while the other one found decreased Mg concentration in lymphocytes and polymorphonuclear cells, but not erythrocytes.[8] Investigation using in vivo ^{31}P nuclear magnetic resonance spectroscopy showed low brain Mg during and between migraine attacks in a few subjects.[11]

We postulated that changes in serum IMg^{2+} rather than in total serum Mg or tissue levels of Mg may reflect metabolic disturbances in a migraine attack. Until recently there was no direct way to precisely determine serum IMg^{2+} levels. Development of an ion-selective electrode for IMg^{2+},[12,13] allowed us for the first time to precisely and rapidly measure levels of IMg^{2+} in the serum of patients with various types of headaches.

SUBJECTS AND METHODS

After an informed consent 121 consecutive patients seen at a headache clinic had their blood drawn anaerobically to maintain a normal pH. Patients who had multiple or serious medical problems or were unable to rate their headache intensity were not included in this study. The laboratory personnel were blinded as the blood samples were not accompanied by any clinical information. Serum levels of IMg^{2+} and ICa^{2+} were measured using ion-selective electrodes with a NOVA Biomedical Stat Profile 8 Analyzer.[12,13] The accuracy of these electrodes is 97-100%.[12,13] Total Mg in the serum was determined by atomic absorption spectroscopy and a Kodak DT-60 Ektachem Analyzer, which yield identical results.[13] Percent IMg^{2+} ($\%IMg^{2+}$) and ICa^{2+}/IMg^{2+} ratios were calculated. Mean values ± S.E.M. were calculated and compared for statistical

significance by a non-paired Student's t-test, ANOVA and Scheffe's contrast test, where appropriate. A P value of less than 0.05 was considered significant.

An attempt was made to classify all patients according to the IHS criteria, but of 121 patients 18 (15%) were not classifiable. Twelve of these 18 patients fulfilled criteria for migraine headache, but the headache was continuous (they arguably could be classified as having status migrainosus). We selected for comparison 2 groups of patients. Patients in both groups had a severe headache within 24 hours of blood sampling. Severe headache was defined as greater than 5 on a verbal scale of I to 10. Thirty-three patients who were in the first group suffered from intermittent migraines, while the 13 patients in second group had continuous, daily headaches. In the continuous group 9 patients had nonclassifiable headaches of migrainous type and 4 patients had a daily chronic tension-type headache. The duration of headaches in the continuous group was I month in 3 and 5 months in I patient, while the rest had them for over a year. Sixty healthy (headache-free) faculty, staff and students volunteered to serve as controls.

RESULTS

Mean serum levels of IMg^{2+}, ICa^{2+}, $\%IMg^{2+}$ and $ICa2+/IMg^{2+}$ are shown in Table 1 and Figure 1. Mean values of IMg^{2+}, total Mg and ICa^{2+}/IMg^{2+} are compared in Figure 1. Only three of 13 patients (23%) in the continuous group had a low IMg^{2+} level, while 14 of 33 (42%) in the intermittent group had low IMg^{2+} levels ($P<0.01$, chi-square). When patients with intermittent migraines were divided into subgroups with normal and low IMg^{2+} levels they formed two distinct groups. The group with a low serum IMg^{2+} also had a high ICa^{2+}/IMg^{2+} ratio. The patients with a continuous headache and a sub-group of patients with intermittent migraines had no significant disturbance of IMg^{2+} or $ICa2+/IMg^{2+}$ ratios, but tended to show lowered $\%IMg^{2+}$ relative to total Mg concentration (Table 1). The other subgroup of patients with intermittent migraines had a low IMg^{2+} level and a high ICa^{2+}/IMg^{2+} ratio as well as lowered $\%IMg^{2+}$. Total serum Mg levels were normal in all groups, but patients with intermittent migraines and a low IMg^{2+} level had significantly lower total Mg levels compared to other migraine subgroups.

DISCUSSION

The clear difference in serum IMg^{2+} values between patients with migraine attacks and continuous headaches suggests a different mechanism of pathogenesis of headaches in these two groups. One of several possible ways for Mg to affect the development of headaches is through its effect on vascular tone.[6] It has been long suggested that migraine pathogenesis may involve both cerebral vasospasm and vasodilatation.[6,7,14] Recently, a serotonin hypothesis has become more popular.[15--17] Modulation of serotonin receptors is now thought to be an important step in the development of migraines. Both the vascular and the serotonin aspects of migraine pathogenesis can be influenced by Mg. Experimentally, vasoconstriction is

Table 1
Mean Values ± S.E.M. for patients with a continuous headache and during an intermittent migraine attack. These two groups are sub-divided into those with low and normal serum IMg^{2+} levels.
Patients with a severe, continuous headache or a severe migraine attack within 48 hours of blood sampling were selected from 121 consecutive headache patients.

Group	N	Img^{2+} (mM)	Ica^{2+} (mM)	Total Mg (mM)	% IMg^{2+}
Controls	60	0.59 ± 0,005	1.19 ± 0.015	0.81 ± 0.008	71.6 ± 0.58
Intermittent Migraine	33	0.556 ± 0,009*	1.23 ± 0.007	0.836 ± 0.012	66.5 ± 0.63*
A. Low IMg^{2+}	14	0.50 ± 0.007+	1.22 ± 0.014	0.78 ± 0.015**	64.6 ± 0.75*
B. Normal IMg^{2+}	19	0.611 ± 0.017	1.24 ± 0.007	0,876 ± 0.012	67.9 ± 0.83*
Continuous Severe	13	0.567 ± 0.013	1.22 ± 0.008	0.86 ± 0.019	66.0 ± 1.03*
A. Low IMg^{2+}	3	0.517 ± .003++	1.22 ± 0.027	0.846 ± 0.013	62.0 ± 1.00+
B. Normal IMg^{2+}	10	0.582 ± 0.013	1.22 ± 0.007	0.861 ± 0.024	67.6 ± 0.98*

*Significantly diff. from controls (<0.01); +Sig, diff. from all groups except low continuous severe (p<0.01).
** Sig. diff. from all migraine subgroups (p<0.01). ++Sig, diff. from all groups except low intermittent migraine (p<0.01).

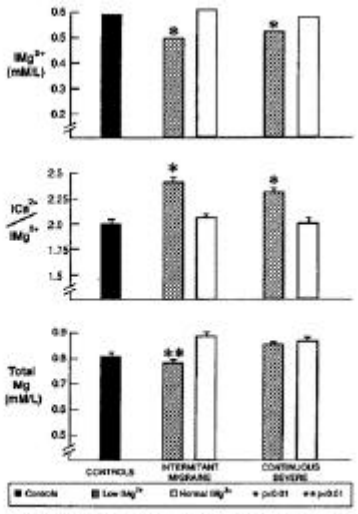

Fig. 1—Comparison of serum IMg^{2+} levels, ICa^{2+}/IMg^{2+} ratios and serum total Mg levels in patients with low and normal IMg^{2+}. Bars- mean values ± S.E.M.

facilitated by a lowering of the extracellular levels of IMg^{2+} decreasing the gradient of IMg^{2+} or, possibly, by increasing the gradient of ICa^{2+}/IMg^{2+} ratio across the vascular smooth muscle cell membranes,[18-22] thus causing a rise in intracellular free Ca^{2+}.[23,24] IMg^{2+} levels may influence calcium channels and the intracellular ICa^{2+} levels, which in turn control vascular tone.[25,26] This may be the mechanism of headache prevention by calcium channel blockers.[27-29] Serotonin receptor activity could clearly be affected by IMg^{2+} concentration,[30-32] although the role of serotonin receptors in the development of migraine remains unclear. A low IMg^{2+} level could also facilitate the development of spreading depression of Leão,[33] which is thought to underlie the phenomenon of migraine aura.[34] IMg^{2+} could affect the development of headaches by modulation of N-methyI-D-aspartate (NMDA) re-ceptors.[35,36] Lastly, the release of several other neurotransmitters is also controlled by the ICa^{2+}/ IMg^{2+} ratio.[37] Thus, it is conceivable that changes in the ICa^{2+}/IMg^{2+} ratio may therefore be more important in the development of headaches than IMg^{2+} or the total Mg level.

Our findings support and possibly combine both the vascular and the serotonin theories of migraine pathogenesis.

Artificially lowering the Mg content of cerebral blood vessels in vivo and in vitro induces calcium-mediated vasospastic responses, while elevation in $[Mg^{2+}]$ reduces vascular tone.[18-22] A lowering of IMg^{2+} and an elevation of the ICa^{2+}/IMg^{2+} ratio would have three effects on serotonin action: 1. an increased affinity for serotonin cerebral vascular muscle receptor sites;[30-32] 2. a potentiation of cerebral vasoconstriction induced by serotonin;[18-22] and 3. a facilitation of 5-HT release from neuronal storage sites.[37] Finally, a decrease in serum and tissue Mg, at intermittent times, as has been reported by several groups[8-11] could create a situation favoring vascular vasodilatation followed by a sustained contraction mediated by endothelium-derived relaxant factors.[38-40] The latter would explain the biphasic vasomotor changes in cerebral vascular tone seen in migraine.[6,7,17,41,42]

The deficit in serum IMg^{2+} levels or an increase in the ICa^{2+}/IMg^{2+} ratio may, thus, be two of the triggering factors that set off a migraine attack in susceptible individuals. Serotonin receptors (and possibly other neurotransmitters) and blood vessels are the likely mediators of the clinical syndrome that follows. Alternatively, it is possible that this alteration of Mg metabolism is not the initiating event, but is secondary to other biochemical phenomena. Frequent, sequential measurements of serum IMg^{2+} levels and ICa^{2+}/IMg^{2+} ratios immediately before, during and after migraine attacks would be difficult to do, but could provide this information.

The susceptibility to migraines, at least in part, could be genetic in nature as suggested by the high incidence offamilial clustering of this condition and by the twin studies.[43,44] Cellular Mg content and magnesium metabolism are under genetic control as well,[45] and it is conceivable that the heredity of migraines and magnesium metabolism overlap.

The observed normal level of IMg^{2+} in 10 out of 13 patients with continuous headaches indicates that the process of transformation of intermittent headaches into a continuous one either does not involve a disturbance of Mg metabolism or is accompanied by a normalization of Mg metabolism. Continuous headaches may represent a type of central pain syndrome where more subtle neurotransmitter changes are involved in pain perception and its perpetuation. Clinical experience supports this speculation. Abortive medications (analgesics, ergots, combinations of drugs) are usually ineffective in this type of headaches. Overuse of abortive medications is one of the possible causes of transformation of intermittent headaches into a continuous one.[46-48] Of our 13 patients with continuous headaches 4 were regularly taking this type of medication.

In conclusion, this paper demonstrates that in 42% of patients with an acute migraine attack serum IMg^{2+} levels are low, while the ICa^{2+}/IMg^{2+} ratio is high. By comparison only 23% of patients with continuous headaches had a low serum IMg^{2+} level. The use of an ion-selective electrode for Mg^{2+} should allow further elucidation and differentiation of the pathogenesis of headaches by determining serum IMg^{2+}, ICa^{2+}, $\%IMg^{2+}$ and ICa^{2+}/IMg^{2+} in large groups of patients with various headache types. This may lead to the development of specific therapies for each headache type. Mg supplementation may be an effective treatment for one of the sub-groups of patients.

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