

Why all migraine patients should be treated with magnesium

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Abstract Magnesium, the second most abundant intracellular cation, is essential in many intracellular processes and appears to play an important role in migraine pathogenesis. Routine blood tests do not reflect true body magnesium stores since <2 % is in the measurable, extracellular space, 67 % is in the bone and 31 % is located intracellularly. Lack of magnesium may promote cortical spreading depression, hyperaggregation of platelets, affect serotonin receptor function, and influence synthesis and release of a variety of neurotransmitters. Migraine sufferers may develop magnesium deficiency due to genetic inability to absorb magnesium, inherited renal magnesium wasting, excretion of excessive amounts of magnesium due to stress, low nutritional intake, and several other reasons. There is strong evidence that magnesium deficiency is much more prevalent in migraine sufferers than in healthy controls. Double-blind, placebo-controlled trials have produced mixed results, most likely because both magnesium deficient and non-deficient patients were included in these trials. This is akin to giving cyanocobalamin in a blinded fashion to a group of people with peripheral neuropathy without regard to their cyanocobalamin levels. Both oral and intravenous magnesium are widely available, extremely safe, very inexpensive and for patients who are magnesium deficient can be highly effective. Considering these features of magnesium, the fact that magnesium deficiency may be present in up to half of migraine

patients, and that routine blood tests are not indicative of magnesium status, empiric treatment with at least oral magnesium is warranted in all migraine sufferers.

Keywords Migraine · Aura · Deficiency · Intravenous · Magnesium

Introduction

This article will attempt to convince the reader that all migraine sufferers should receive a therapeutic trial of magnesium supplementation.

Pathophysiology

Magnesium is an essential element that controls normal adenosine triphosphate function, glucose metabolism, and a variety of other cellular functions. It is also involved in skeletal and cardiac muscle function and cytoskeleton contraction; magnesium is absorbed through intestinal epithelial channels and reabsorbed with calcium in the thick ascending limb of the kidneys and also through channels in the distal tubule. The $\text{Ca}^{2+}/\text{Mg}^{2+}$ sensing receptor detects levels of ionized calcium (ICa^{2+}) and magnesium (IMg^{2+}) and regulates these levels by controlling parathyroid hormone secretion. Of the total body magnesium, 67 % is found in the bone and 31 % is located intracellularly. Only the remaining 2 % is in the measurable, extracellular space, and therefore the levels found on routine blood tests do not reflect true body stores.

Due to the lack of accurate testing, hypomagnesemia, a common deficiency of magnesium, is often overlooked. Magnesium deficiency is found in patients with chronic

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medical illnesses, including cardiovascular disease, diabetes, pre-eclampsia, eclampsia, sickle cell disease, and chronic alcoholism. Hypomagnesemia usually occurs in conjunction with other electrolyte abnormalities such as hypokalemia, hyponatremia, hypocalcemia, and hypophosphatemia. Patients with refractory hypocalcemia and hypokalemia should also be evaluated for possible hypomagnesemia. Diuretics, digoxin, aminoglycosides, amphotericin, and cisplatin can also cause magnesium deficiency (Innerarity 2000). Hypomagnesemia is very common, occurring in about 14.5 % of the general population (Schimatschek and Rempis 2001). While the exact mechanism remains unclear, it is believed that migraines are caused by genetic abnormalities that cause hyperexcitability of the nervous system. The trigeminal nerve terminals are also involved in migraine generation and are known to release neurotransmitters such as substance P, neurokinin A (NKA), and calcitonin gene-related peptide (CGRP), which bind to the receptors on intracranial blood vessels. This causes vasodilation, mast cell degranulation, increased vascular permeability and blood vessel edema, plasma protein extravasation, and sterile inflammation. The trigeminal nerve is then reactivated causing the pain experienced during a migraine. Cortical spread depression (CSD) is a phenomenon that can explain the aura of migraines (Strong 2003). Aura consists of a variety of sensory warning signs or symptoms, such as blind spots, flashes of light, or tingling sensations in the hands or face. CSD occurs when the cerebral cortex is stimulated by chemical or electric signals. This stimulation leads to an excitation of the cerebral cortex, which is followed by extended depolarization of cortical neurons that gradually spreads through the cortex. This process is followed by a wave of oligemia. CSD has been documented by magnetic resonance imaging (Hadjikhani et al. 2001), epidural electrophysiological recordings (Fabricius et al. 2006; Strong et al. 2002), and intracortical multiparametric electrodes (Mayevsky et al. 2006).

Genetic factors are clearly operational in the susceptibility to migraine headaches. Magnesium absorption and excretion is also influenced by genetic factors. It is possible that there is an overlap between the genetics of migraine and magnesium metabolism.

Those who suffer from migraines may excrete excessive amounts of magnesium due to stress, producing a deficiency of magnesium (Durlach 1976). Migraines have also been linked with low levels of magnesium in the brain interictally (Ramadan et al. 1989) as well as in the cerebrospinal fluid (Jain et al. 1985). A lowered magnesium level in cellular concentrations could be an indicator of low cerebral levels, which could add to a lowered threshold for migraine headaches. A magnesium load test study (Trauninger et al. 2002) revealed that greater retention of

magnesium occurred in patients suffering from migraines compared to healthy controls, suggesting a systemic deficiency. A 2-week trial revealed that when migraine patients drank water with magnesium, their total magnesium significantly increased in erythrocytes. Red blood cell magnesium assays more accurately assess magnesium deficiency and have wider commercial availability (Touitou et al. 1987). However, even this measure is not entirely accurate and, just like serum levels, is only useful when it is low.

Magnesium deficiency has been associated with CSD (Strong et al. 2002), neurotransmitter release (Coan and Collingridge 1985), platelet aggregation (Baudouin-Legros et al. 1986), and vasoconstriction (Altura and Altura 1982, 1989). Substance P is released as a result of magnesium deficiency, which is hypothesized to act on sensory fibers and produce headache pain (Innerarity 2000). External magnesium may help to diminish various aspects of neurogenic inflammation. It is involved in the control of NMDA glutamate receptors, which play an important role in pain transmission within the nervous system (Foster and Fagg 1987) and in regulation of cerebral blood flow (Huang et al. 1994). The NMDA receptor plays a role in initiation and spread of CSD. Studies have shown that Mg^{2+} can block the CSD induced by glutamate. The combination of intravenous magnesium sulfate and intravenous prochlorperazine (a dopamine D2 receptor antagonist) was successfully used to end an extended aura in two patients (Rozen 2003).

Many preclinical and clinical findings have demonstrated a positive correlation between migraine and serum levels of CGRP, a neuropeptide. Serum levels return to normal when the migraine pain subsides. The development of CGRP antagonists has been of interest since they lack direct vasoconstrictor activity, thus giving a clear advantage over triptans, which are currently used in acute migraine treatment but contraindicated in patients with cardiovascular risk factors. Erythrocyte magnesium levels increased significantly after magnesium sulfate infusion in women with Raynaud's phenomenon but not in the controls (Myrdal et al. 1994).

Nitric oxide (NO) is a signaling molecule, involved in the regulation of cerebral and extracerebral blood flow and arterial diameters. It also plays a role as a synaptic modulator and is involved in nociceptive processing (Meller and Gebhart 1993). NO is suggested to be a key molecule in the development of migraines (Olesen et al. 1994) by the fact that glyceryl trinitrate (GTN), known to induce headaches, acts as an exogenous NO donor. Other evidence has suggested that the effect of NO in migraine pathogenesis may not be a vascular one (Goadsby 2006), but instead NOS blockade may inhibit trigemino-cervical complex fos expression (Hoskin et al. 1999). NO production can be

modulated by changes in magnesium levels in that low levels would be expected to inhibit the production of NO (Altura and Altura 1987).

Another key molecule in migraine pathogenesis is serotonin, a potent cerebral vasoconstrictor released from platelets during an attack; it also promotes nausea and vomiting. A decrease in the serum ionized magnesium level and an elevation of the serum ratio of ICa^{2+} to IMg^{2+} may increase the likelihood for cerebral vascular muscle serotonin receptor sites, potentiate cerebral vasoconstriction induced by serotonin, and facilitate serotonin release from neuronal storage sites (Peters et al. 1988). Vasoconstriction produced from serotonin can be blocked by pretreatment with Mg^{2+} , a safe and inexpensive treatment (Goldstein and Zsoter 1978).

There is a lack of accurate and reliable methods to assess magnesium content, and serum and tissue magnesium levels do not reflect total magnesium levels. The development of an ion-selective electrode for the measurement of ionized magnesium has allowed a more precise measurement of the biologically active ionized magnesium (Altura et al. 1992). Of 500 patients with various headache syndromes, 29 % had decreased levels of ionized magnesium (normal adult IMg^{2+} ranges from 0.54 to 0.65 mmol/L) (Mauskop et al. 1995a). Another study (Mauskop et al. 1996) showed 50 % of migraine patients with lowered magnesium. Infusion of 1 g of intravenous magnesium was correlated to basal serum IMg^{2+} level in both studies. Of those patients with sustained pain relief (over 24 h), 89 % had a low serum IMg^{2+} level; only 16 % who had no relief had a low IMg^{2+} level. However, total magnesium levels in all patients were within normal parameters. Migraine without aura, cluster, chronic migraine and chronic tension-type headaches showed the lowest serum IMg^{2+} levels during headache and prior to administration of intravenous magnesium sulfate.

Therapeutic trials

Two double-blind, placebo-controlled randomized trials have shown therapeutic efficacy of magnesium supplementation in headache patients. The first study was conducted in 24 women with menstrual migraines. Women received two cycles of magnesium or placebo taken daily from ovulation to the first day of flow. Patients receiving active treatment had a significant reduction of the frequency of headache ($p < 0.1$) and total pain index ($p < 0.03$) and showed improvement of the Menstrual Distress Questionnaire score (Facchinetti et al. 1991). A larger double-blind, placebo-controlled randomized study also showed significant improvement in patients on active therapy (Peikert et al. 1996). The reduction of the

frequency of attacks in the magnesium group (41.6 %) was much greater than in the placebo group (15.8 %). The active group received 600 mg of trimagnesium dicitrate in a water-soluble granular powder taken every morning. Diarrhea was present in 18.6 % and gastric irritation in 4.7 % of patients in the test group. A third trial using a different magnesium salt showed no effect of oral magnesium on migraine (Pfaffenrath et al. 1996). However, diarrhea occurred in almost half of the patients receiving magnesium compared to a quarter of patients on placebo. This was clearly a poorly absorbed magnesium salt and no improvement could be expected since magnesium was not absorbed.

Some trials have also shown that intravenous magnesium to be effective in the treatment of acute migraine. In a pilot study (Mauskop et al. 1995b), 40 consecutive patients presenting with an acute migraine to a headache clinic were treated with an intravenous infusion of 1 g of magnesium sulfate. Of patients who had serum IMg^{2+} levels below 0.54 mmol/L, 86 % had relief of pain and associated symptoms that continued for over 24 h. Only 16 % of patients who had serum IMg^{2+} levels >0.54 mmol/L experienced a similar degree of relief. Although this study was not double blind, the researchers had no access to the information about patients' IMg^{2+} levels for 2 weeks after the clinical assessment was completed.

A double-blind study of 120 migraine patients presenting to an emergency room showed that patients with migraine with aura who received magnesium sulfate showed a significant improvement in pain and symptoms than compared to those who received placebo (Bigal 2002). There were no significant changes in pain relief or nausea between treatment and placebo groups in patients with migraine without aura. In these patients, there was a significant decrease of intensity of photophobia and phonophobia.

Another emergency room study (Corbo et al. 2001) involved 44 patients with acute migraine who received either 20 mg of metoclopramide plus 2 g of intravenous magnesium sulfate or 20 mg of metoclopramide plus placebo in 15-min intervals for up to three doses. In this trial, results favored the placebo group at the final rating. The authors have suggested that adding magnesium to metoclopramide might somehow decrease the efficacy of the drug in decreasing migraine pain.

In the third double-blind placebo-controlled emergency room study (Cete et al. 2005), patients received 10 mg of metoclopramide, 2 g of magnesium sulfate, or placebo. All three groups showed more than a 25-mm improvement in the standard visual analog scale (VAS) score at 30 min, which was the primary end point. Recurrence rates within 24 h were similar; however, the placebo group had a greater need for additional rescue medication.

Magnesium was also found to be effective for the treatment of cluster headaches (Mauskop et al. 1995a, b). Of the 22 consecutive patients with cluster headaches treated with 1 g of magnesium sulfate, 41 % reported meaningful relief after treatment. Meaningful relief was defined as a complete cessation of attacks or relief for more than 3 days. A study of 270 women, 61 of whom had menstrually related migraines, showed that magnesium deficiency was highest (45 %) during menstrual attacks (Mauskop et al. 2002). Another study (Abraham and Lubran 1981) suggested that red blood magnesium deficiency might explain the symptoms of premenstrual syndrome, which could include migraine.

Hypomagnesemia has also been documented in pediatric migraine. When compared with healthy control, pediatric migraine patients (with and without aura) showed a significant reduction in serum, red blood cells, and mononuclear blood cell magnesium concentration (Mazzotta et al. 1999, Soriani et al. 1995). In a randomized, double-blind, placebo-controlled trial (Wang et al. 2003), children and adolescents ages 3–17 who were given magnesium oxide showed a statistically significant trend toward headache frequency reduction, although the primary outcome measure was not significantly different.

Summary

A multitude of studies have proven the presence of magnesium deficiency in migraine patients. While double-blind, placebo-controlled trials are the gold standard in proving the efficacy of a drug, conducting these trials in deficiency states is completely illogical. For example, vitamin B12 deficiency is known to cause peripheral neuropathy. No reasonable person would insist on conducting double-blind trials of vitamin B12 supplementation in a group of patients with peripheral neuropathy regardless of their cyanocobalamin level. The same should apply to migraine sufferers. If they are found to be deficient by a reliable test, they should be given oral magnesium, and if it is ineffective or not tolerated, and intravenous infusion. Unfortunately, we do not have a reliable test. Serum levels are entirely inaccurate, while RBC magnesium is more reliable but expensive, and both are mostly useful if they show a deficiency. Considering that up to 50 % of patients with migraines could potentially benefit from this extremely safe and very inexpensive treatment, it should be recommended to all migraine patients. The daily recommended dose is 400 mg of magnesium oxide, chelated magnesium (magnesium aspartate, diglycinate, gluconate, etc.), or another magnesium salt. If the initial dose is ineffective and hypomagnesemia is strongly suspected (in addition to migraines, patient has cold extremities,

premenstrual syndrome, and leg or foot muscle cramps) the dose can be doubled. Dosage is limited due to side effects such as diarrhea and abdominal pain. For patients who do not tolerate or absorb oral magnesium, monthly intravenous magnesium is recommended for prophylactic migraine treatment. As far as an acute treatment, again considering that up to 50 % of patients during an acute migraine have low ionized magnesium levels and that it is a remarkably safe and inexpensive treatment, intravenous infusion should be considered as the first parenteral option.

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