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Role of magnesium in the pathogenesis and treatment of migraine

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Magnesium is an important intracellular element that is involved in numerous cellular functions. Deficiencies in magnesium may play an important role in the pathogenesis of migraine headaches by promoting cortical spreading depression, alteration of neurotransmitter release and the hyperaggregation of platelets. Given this multifaceted role of magnesium in migraine, the use of magnesium in both acute and preventive headache treatment has been researched as a potentially simple, inexpensive, safe and well-tolerated option. Studies have shown that preventive treatment with oral magnesium and acute headache treatment with intravenous magnesium may be effective, particularly in certain subsets of patients. In this review, the pathogenesis of migraine will be discussed, with an emphasis on the role of magnesium. Studies on the use of intravenous and oral magnesium in migraine treatment will be discussed and recommendations will be made regarding the use of magnesium in treating migraine headaches.

Keywords: headache • intracellular magnesium • ionized magnesium • magnesium • magnesium deficiency • migraine • migraine pathogenesis • serum magnesium

Magnesium is a vital intracellular element that is involved in numerous cellular functions. Deficiencies in magnesium may play an important role in the pathogenesis of migraine headaches, by promoting cortical spreading depression (CSD), alteration of neurotransmitter release and the hyperaggregation of platelets. Given this multifaceted role of magnesium in migraine, the use of magnesium in both acute and preventive headache treatment has been studied as a potentially simple, inexpensive, safe and well-tolerated option.

Role of magnesium in human physiology

Magnesium is an essential cation that plays a critical role in a multitude of physiological processes, owing to its central role in normal ATP function and glucose metabolism. It is also necessary for the proper functioning of several ATPases, such as the Na^+/K^+ ATPase, which controls the Na^+ pump. It has powerful membrane-stabilizing properties that are important for the insertion of proteins and the formation of phospholipids [1]. It also contributes significantly to skeletal and cardiac muscle function in that it is vital to cellular cytoskeleton contraction and at the myoneural junction. Magnesium is absorbed through intestinal epithelial channels via a non-vitamin D-dependent process, and reabsorbed with calcium in the thick ascending limb of the kidneys and also by means of specific magnesium transport channels in the distal tubule. [2]. Magnesium homeostasis is maintained by the Ca^{2+}/Mg^{2+} sensing receptor (CASR) [3], which is located in the parathyroid hormone (PTH)-secreting cells of the parathyroid glands and in the nephron segments that are involved in renal calcium and magnesium reabsorption. CASR acts by sensing levels of ionized calcium and magnesium, then regulating these levels by controlling PTH secretion [4,5]. Less than 2% of the total body magnesium is in the measurable, extracellular space and, therefore, the levels found on routine blood testing do not reflect true total body stores [6]. It is the second most abundant intracellular cation, with 31% of total body magnesium located intracellularly and 67% in the bone.

Hypomagnesemia is common: an epidemiological study evaluating an unselected population group of approximately 16,000 people in Germany found that its prevalence (Mg serum level below 0.76 mmol/l) was approximately 14.5%, with higher frequencies observed in females and outpatients [7]. It may be due to decreased intake, decreased gastrointestinal absorption or diarrhea, increased urinary losses, genetic factors [8] or any combination of these

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causes. Deficits in magnesium can also be seen in any chronic medical illness, including cardiovascular disease, diabetes, preeclampsia, eclampsia, sickle cell disease and chronic alcoholism [9]. Low magnesium has also been noted in patients with end-stage renal disease who suffer from hemodialysis headache [10]. Clinical symptoms include apathy, depression, delirium, seizures, paresthesias, tremors, general weakness, premenstrual syndrome, cold extremities, leg and foot cramps and ventricular arrythmias. Hypomagnesemia frequently occurs in conjunction with other electrolyte abnormalities, such as hypokalemia, hyponatremia, hypocalcemia and hypophosphatemia [11]. Since serum levels do not accurately reflect total body stores of magnesium, patients who actually have low ionized, or free, magnesium levels may have normal serum levels. Therefore, urinary fractional excretion of magnesium may be a better method of assessing for hypomagnesemia in patients in whom this is clinically suspected. Similarly, the magnesium load test, in which the total excretion of urinary magnesium over 24 h is calculated after the administration of a loading dose of oral magnesium, is an indirect but reliable way of assessing the total body magnesium status [12–14]. Hypomagnesemia should also be strongly considered in patients with chronic illnesses, as well as in those with refractory hypocalcemia and hypokalemia. Medications such as diuretics, digoxin, aminoglycosides, amphotericin and cisplatin are also associated with hypomagnesemia [15].

By contrast, hypermagnesemia is uncommon given the kidney's ability to respond quickly to high serum levels. Causes of high magnesium levels include increased intake, decrease renal excretion and redistribution with acidosis. Clinical symptoms of hypermagnesemia include lethargy, confusion, arrhythmias and muscle weakness, and generally occur with severe acute changes or chronic toxicity [6]. Hypermagnesemia resulting from magnesium treatment may also result in a decrease in serum calcium [16,17], which has been associated with increased morbidity and mortality in critically ill patients in intensive care settings [18,19]. Treatment usually involves volume repletion and decreasing intake. Severe cases and cardiac arrhythmias resulting from hypermagnesemia can be treated with dialysis and calcium infusions.

Current understanding of migraine pathogenesis

In recent years, significant advances have been made in the understanding of migraine pathophysiology. Although the exact etiology remains to be defined, the current prevailing theories are based on a hyperexcitable 'trigeminovascular complex' and possibly cortex, in patients who are genetically predisposed to migraine. In these susceptible individuals, the trigeminovascular neurons release neurotransmitters, such as calcitonin gene-related peptide (CGRP) and substance P, when headache triggers are encountered. This leads to vasodilation, mast cell degranulation, increased vascular permeability and blood vessel edema, resulting in meningeal neurogenic inflammation. This nociceptive information is transmitted from the periphery, along the trigeminal nerve to the brainstem trigeminal nucleus caudalis and then to thalamic nuclei and the cortex, where migraine pain is ultimately perceived [20]. The locus coeruleus, which contains noradrenergic neurons, the dorsal raphe nuclei, which consist of serotonergic neurons, and the periaqueductal gray also play modulatory roles in the transmission of pain [21].

The aura of migraine can be explained by the phenomenon of CSD. In experimental animals and in human neocortical and hippocampal tissue *in vitro*, CSD occurs when an electric or chemical stimulus is applied to the cerebral cortex, resulting in an excitation followed by a prolonged depolarization of cortical neurons that gradually spreads across the cortex. This wave of depolarization occurs in conjunction with a wave of oligemia [22–26]. Activation of the *N*-methyl-D-aspartate (NMDA) receptor subtype is required to trigger CSD in rat cerebral cortex [27] and in human neocortical tissues [28]. A similar phenomenon is hypothesized to occur spontaneously in humans, producing the aura. Recent evidence obtained from functional magnetic resonance imaging [29], epidural electrophysiological recordings [30–32] and intracortical multiparametric electrodes [33] have supported this hypothesis. The mechanism by which the headache phase develops from the aura is unknown and somewhat controversial, but the first phase may be related to the cortical release of CGRP, nitric oxide, arachidonic acid or various ions and their effects via the trigeminal nerve into the brainstem and back to the dural blood vessels [34,35].

It has been speculated that, during headaches, migraine sufferers excrete excessive amounts of magnesium as a result of stress, resulting in transient serum hypomagnesemia [36]. Conversely, it may be possible that stress causes magnesium excretion, leading to hypomagnesemia, which triggers a migraine. Migraine has also been associated with low levels of magnesium in the cerebrospinal fluid [37], and *in vivo* ^{31}P nuclear magnetic resonance spectroscopy (MRS) has demonstrated low magnesium in the brain during attacks and interictally in some patients [38]. Another study which utilized ^{31}P MRS imaging demonstrated reduced Mg^{2+}concentration in the posterior brain, including the occipital cortex, of patients with hemiplegic migraine [39]. In this study, decreases in posterior brain Mg^{2+} concentration were also correlated with the severity of neurologic complaints, according to trend analyses. However, there was actually a trend towards increased Mg^{2+} concentrations in patients with migraine without aura. The authors attributed this finding to a possible decrease in intracellular potassium concentration, which can occur in neuronal tissue prone to hyperexcitability [40]. Phosphorus MRS was used in a third study to assess the brain cytosolic free magnesium concentration and the free energy released by ATP hydrolysis (an indicator of the cell's bioenergetic condition) in patients with migraine or cluster headaches during attack-free periods [41]. Both cytosolic free Mg^{2+} and free energy released by ATP hydrolysis were reduced in all subgroups of patients with migraine and cluster headaches, supporting the authors' hypothesis that a reduction in free Mg^{2+} in tissues with mitochondrial dysfunction is secondary to the bioenergetic deficit.

During attacks, serum Mg^{2+} levels are reduced [42], and levels in saliva have been shown to be decreased during attacks and interictally in migraineurs (with and without aura) compared with controls [42,43]. Reductions in cellular concentrations of magnesium at the peripheral level could be an indicator of low cerebral levels, which might contribute to a lowered threshold for migraine headaches [38]. One study, which utilized the magnesium load test, showed that magnesium retention occurred in patients with migraine after oral loading with 3000 mg of magnesium lactate during a 24-h interictal period, suggesting a systemic magnesium deficiency [44]. Other interictal studies on serum [36,42,43,45–47], plasma [48,49] and intracellular [46–51] Mg^{2+} levels in migraineurs and patients with tension-type headache (TTH) have yielded inconsistent results. However, interictal levels of red blood cell (RBC) magnesium have been shown to be decreased in migraineurs with [50] and without aura [47,48], as well as in juvenile migraine patients with and without aura [52]. These results were corroborated by a study that showed low total magnesium in erythrocytes and low ionized magnesium in lymphocytes in migraine patients, both of which increased significantly after a 2-week trial of drinking mineral water containing 110 mg/l magnesium [53]. Therefore, given its commercial availability, the RBC magnesium assay may be a good way of assessing for deficiency [52–54].

Role of magnesium in migraine pathophysiology

Magnesium has been hypothesized to play a role in several different aspects of migraine pathogenesis as previously described. Magnesium deficiency has been associated with CSD [55], neurotransmitter release [56], platelet aggregation [57] and vasoconstriction [58,59], all of which are relevant features of our current understanding of migraine pathophysiology. Also, magnesium deficiency results in the generation and release of substance P [60], which is believed to act on sensory fibers and produce headache pain [20]. Therefore, external magnesium may beneficially target various aspects of the neurogenic inflammation that occur during migraine by counteracting vasospasm, inhibiting platelet aggregation, stabilization of cell membranes and reducing the formation of inflammatory mediators. In this section, magnesium's contribution to the various facets of migraine pathogenesis will be discussed more specifically.

NMDA receptors

Magnesium is closely involved in the control of NMDA glutamate receptors, which play an important role in pain transmission within the nervous system [61] and in the regulation of cerebral blood flow [62]. Magnesium ions 'plug' the NMDA receptor [56] and prevent calcium ions from entering the cell. As such, reducing magnesium levels facilitates activation of the NMDA receptor, thus allowing calcium to enter the cell and exert its effects both on neurons and cerebral vascular muscle. Magnesium can therefore be considered an antagonist at several important sites in the NMDA receptor complex.

The NMDA receptor is known to play an important role in the initiation and spreading of cortical depression [27,63]. Studies have shown that Mg^{2+} can block the spreading cortical depression induced by glutamate and that CSD is more readily initiated with low levels of Mg^{2+} in the cerebral cortex [55], and chemical stimuli that induce experimental CSD include decreased extracellular Mg^{2+} [64,65]. In animal models, glutamate-induced CSD in chick retinas has been shown to be inhibited by magnesium chloride [66], and CSD in rats induced by potassium chloride and cardiac arrest-induced anoxic depolarization can be suppressed by intravenous magnesium sulfate [67]. The relationship between magnesium and the NMDA receptor has been further corroborated by studies showing that Mg^{2+} may decrease the intensity of morphine-induced drug dependence in rats by decreasing the glutamate effect on those receptors in the brain [68,69].

Based on the above hypothesis and the idea that migraine aura may also be due in part to dopamine receptor hypersensitivity [70], the combination of intravenous magnesium sulfate and intravenous prochlorperazine (a dopamine D_2 receptor antagonist) was successfully used to abort a prolonged aura in two patients, as described in a case report [71].

There is also accumulating evidence that NMDA receptor mechanisms play an important role in nocicepitive processes and the resulting neuroplastic changes in trigeminal nociceptive neurons, further suggesting that NMDA antagonists may be useful as analgesics and in the treatment of persistent injury and pain [72,73]. While the use of magnesium in such situations can be extrapolated from this evidence, there is no direct substantiation of this as yet.

Calcitonin gene-related peptide

Calcitonin gene-related peptide, a neuropeptide, is believed to play a pivotal role in the pathophysiology of migraine, as preclinical and clinical findings have demonstrated a positive correlation between migraine headache and serum levels of CGRP [74]. CGRP is released from activated trigeminal sensory nerves, dilates intracranial blood vessels and may also increase nociceptive transmission centrally in the brainstem and spinal cord. After migraine pain subsides, levels return to normal. These findings led to the postulation that inhibition of either central or trigeminal CGRP release or CGRP-induced cranial vasodilation might be effective in aborting migraine attacks. The development of CGRP antagonists has been of particular interest since they lack direct vasoconstrictor activity, thus offering a distinct advantage over triptans, which are the current gold standard in acute migraine treatment, but contraindicated in patients with cardiovascular risk factors.

Magnesium has been shown to have an effect on circulating levels of CGRP. One study evaluated the effects of treatment with intravenous magnesium sulfate on 12 women with pronounced primary Raynaud's phenomenon (PRP) and 12 healthy females [75]. There were no significant differences in baseline levels of circulating CGRP between the two groups of women. Treatment with magnesium sulfate infusion significantly decreased circulating CGRP in women with PRP, but not the control subjects. Furthermore, erythrocyte magnesium levels increased significantly after magnesium sulfate infusion in women with PRP but not in the controls.

Nitric oxide

Nitric oxide (NO) is a signaling molecule that is synthesized from the guanidonitrogen of L-arginine by the enzyme NO synthase (NOS). It is also involved in the regulation of cerebral and extracerebral blood flow and arterial diameters. In addition, it plays a role as a synaptic modulator and is involved in nociceptive processing [76]. It diffuses through membranes and has several targets. It can also facilitate glutaminergic transmission, possibly through the direct action of NO derivatives on the NMDA receptor, thus augmenting NMDA-evoked currents [77]. NMDA receptor activity is linked to magnesium levels and, CSD as described previously.

Though it was known for many years that glyceryl trinitrate (GTN) can induce headaches, it was only relatively recently determined that GTN acts as an exogenous NO donor and, thus, that NO is a key molecule in the development of migraine [78]. Furthermore, when GTN is administered to migraine patients, they develop a short-lasting headache followed several hours later by a second headache of greater intensity, demonstrating a more profound response to NO as compared with controls, and therefore also supporting the idea that migraineurs are more sensitive to NO [79]. Other evidence supporting the concept that NO mediates headache pain in migraine attacks includes a clinical study in which the nonselective NOS inhibitor N(G)-mono-methyl-L-arginine (L-NMMA) was administered intravenously during a migraine attack [80]. Ten out of 15 patients who received treatment experienced significant pain relief 2 h after administration, compared with two out of 14 control subjects. Improvements in associated symptoms such as photophobia and phonophobia were also noted.

More recently, evidence has suggested that the effect of NO in migraine pathogenesis may not in fact be a vascular one [81]. Inducible NOS (iNOS) has been implicated in migraine pathophysiology [82], and NOS blockade has been reported to inhibit trigemino-cervical complex fos expression [83]. As such, NOS has been a target for migraine treatments in development.

Nitric oxide production can be modulated by changes in magnesium levels, in that low levels would be expected to inhibit the production of NO [84].

Serotonin

Serotonin (5-hydroxytryptamine [5-HT]) is intimately involved in the pathogenesis of migraine. It is known to be a potent cerebral vasoconstrictor, and is released from platelets during an attack of migraine. It also promotes nausea and vomiting. A decrease in the serum ionized magnesium (IMg^{2+}) level and an elevation of the serum ratio of ionized calcium (ICa^{2+}) to IMg^{2+} may increase the affinity for cerebral vascular muscle serotonin receptor sites, potentiate cerebral vasoconstriction induced by serotonin [85] and facilitate serotonin release from neuronal storage sites [86]. In addition, vasoconstriction induced by serotonin can be blocked by pretreatment with Mg^{2+} [87].

Ionized magnesium versus total serum magnesium

Although magnesium deficiency has been suspected to play a role in the pathogenesis of migraine for many years, the lack of simple and reliable ways of measuring magnesium content in various soft tissues presented an obstacle to the advancement of research. Low serum and tissue levels of total magnesium (TMg) have been reported in migraine patients [43,37,38], although some of these findings were controversial in that both normal and low levels of Mg were found in the same tissues of migraine patients. The most likely reason for this inconsistency has been that, although total magnesium levels have been measured, it is the IMg^{2+} level that truly reflects disturbed magnesium metabolism [88]. The development of a specific ion-selective electrode for magnesium has made it possible to accurately and rapidly measure serum ionized magnesium levels in patients with various headache types [88,89].

Of 500 patients with various headache syndromes, 29% had levels of ionized magnesium below 0.54 mmol/l (normal adult IMg^{2+} ranges from 0.54 to 0.65 mmol/l; 95% [CI]) [90]. A study of 40 patients with an acute migraine attack found that 50% of the patients had this abnormality [90]. Efficacy of 1 g of intravenous magnesium in headache treatment was correlated to the basal serum IMg^{2+} level, corroborating these findings [90,91]. Of the patients in whom pain relief was sustained over 24 h, 86% had a low serum IMg^{2+} level; only 16% of patients who had no relief had a low IMg^{2+} level. However, total magnesium levels in all subjects were within normal limits. When headache types were subdivided into migraine without aura, cluster, chronic migraine and chronic TTHs, most showed low serum IMg^{2+} levels during headache and prior to administration of intravenous magnesium sulfate, with cluster headache patients having the lowest basal levels of IMg^{2+} ($p < 0.01$). All subjects also showed high serum ICa^{2+} IMg^{2+} ratios ($p < 0.01$ compared with controls), except those with chronic TTH. Based on these measurements, it has been suggested that the chronic daily headaches can be subdivided into chronic migraine and chronic TTHs based on magnesium levels. Patients with chronic migraine headaches have a much higher incidence of low serum IMg^{2+} than patients with chronic TTHs [92].

Treatment with oral magnesium

Two double-blind, placebo-controlled trials showed therapeutic efficacy of Mg^{2+} supplementation in headache patients. The first was a double-blind, placebo-controlled study of oral magnesium supplementation in 24 women with menstrual migraine that yielded positive results [48]. The supplement consisted of magnesium pyrrolidone carboxylic acid 360 mg taken in three divided doses. Women received two cycles of study medication, taken daily from ovulation to the first day of flow. In addition to a significant reduction of the number of days with headache ($p < 0.1$) and the total pain index ($p < 0.03$), patients receiving active treatment also showed improvement of the Menstrual Distress Questionnaire score. Four patients dropped out of the study, but only one was due to side effects (magnesium-induced diarrhea).

A larger double-blind, placebo-controlled, randomized study involving 81 patients with migraine headaches also showed significant improvement in patients on active therapy [93]. Attack frequency was reduced by 41.6% in the magnesium group and by 15.8% in the placebo group. The active treatment group received trimagnesium dicitrate 600 mg 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 active group; three patients dropped out of the study.

A third placebo-controlled, double-blind trial showed no effect of oral magnesium on migraine [94]. This negative result has been attributed to the use of a poorly absorbed magnesium salt, since diarrhea occurred in almost half of patients in the treatment group.

Most recently, the prophylactic effects of 600 mg/day oral magnesium citrate supplementation in patients with migraine without aura were assessed in a randomized, double-blind, placebo-controlled study [95]. In addition to clinical evaluations, visual evoked potentials (VEPs) were carried out to asses neurogenic mechanisms of action, and brain single-photon emission computerized tomography (SPECT) was undertaken to assess possible vascular mechanisms. Treatment with oral magnesium citrate 600 mg resulted in a significant decrease in migraine attack frequency, severity and P1 amplitude on VEP when compared with pretreatment values. The post/pretreatment ratios of migraine attack frequency, severity and P1 amplitude were found to be significantly lower in the treatment group compared with the placebo group. SPECT studies showed that cortical blood flow increased significantly to the inferolateral frontal, inferolateral temporal and insular regions after magnesium treatment compared with pretreatment. There were no significant changes in blood flow noted after placebo administration. The authors concluded that magnesium might counteract both vascular and neurogenic mechanisms of migraine and would therefore be a good prophylactic treatment for the disorder.

Visual evoked potentials and SPECT have also been performed as part of the assessment of migraine in other studies. One prior study using VEP to evaluate response to migraine treatment showed a statistically larger amplitude and shorter latency of P1 in untreated migraine patients compared with healthy control subjects [96]. Treatment with oral magnesium pidolate resulted in a significant reduction in amplitude compared with the pretreatment level. While some studies using SPECT have shown cerebral blood flow abnormalities during interictal periods as well as during migraine attacks [97–99], others have showed no changes [100,101].

The most prominent adverse effect associated with oral magnesium supplementation is diarrhea. Although diarrhea itself usually prevents the development of magnesium-related toxicity, patients on oral magnesium treatment should be cautioned about excessive intake. Magnesium toxicity is manifest by loss of deep tendon reflexes, followed by muscle weakness. More severe levels of toxicity can lead to cardiac muscle weakness, respiratory paralysis and death. Patients with kidney disease are at higher risk of developing toxicity [102].

Treatment with intravenous magnesium

Acute migraine treatment

Intravenous magnesium has been used in the treatment of acute migraine, although results from studies examining its use in this context have been conflicting. In a pilot study, 40 patients received intravenous magnesium sulfate after a blood sample was drawn to measure IMg^{2+} levels [90]. An 85% correlation between the clinical response and the levels of serum IMg^{2+} was found ($p < 0.01$). Of the patients who had serum IMg^{2+} levels below 0.54 mmol/l, 86% had relief of pain and associated symptoms that was sustained over 24 h. By contrast, of the patients who had serum IMg^{2+} levels greater than 0.54 mmol/l, only 16% experienced a similar degree of relief. Although the study was not double-blinded or placebo-controlled, both the researchers and subjects were blinded to the IMg^{2+} levels, since the clinical evaluation and treatment were performed well before the laboratory results were known. Later, another study showed that magnesium sulfate 1 g resulted in rapid headache relief in patients with low serum IMg^{2+} levels [91].

In another randomized, single-blind, placebo-controlled trial, 30 patients with moderate-to-severe migraine attacks received either intravenous magnesium sulfate 1 g or 10 ml of saline intravenously [103]. Patients in the placebo group who continued to have pain, nausea or vomiting after 30 min were then given magnesium sulfate 1 g. Treatment was superior to placebo in terms of both response rate (100% for magnesium sulfate vs 7% for placebo) and pain-free rate (87% for magnesium sulfate and 0% for placebo). Although 87% had mild side effects including flushing and a burning sensation in the face and neck, none required discontinuation of treatment. Furthermore, none of the subjects reported headache recurrence during the 24 h after treatment.

The efficacy of magnesium sulfate 1 g on the pain and associated symptoms in patients with migraine without aura and migraine with aura were assessed in a randomized, double-blind, placebo-controlled study [104]. Pain relief was assessed with seven analgesic parameters, and an analog scale was used to measure nausea, photophobia and phonophobia. There were no significant differences in pain relief or nausea between treatment and placebo in patients with migraine without aura, although a significant lower intensity of photophobia and phonophobia in patients receiving magnesium sulfate was noted. However, patients with migraine with aura who received magnesium sulfate showed a statistically significant improvement in pain and all the associated symptoms when compared with those who received placebo.

Two studies have been conducted in an emergency room setting. In the first, a randomized, double-blind, placebo-controlled study, 44 subjects with acute migraine (42 of whom were women) received either metoclopramide 20 mg plus intravenous magnesium sulfate 2 g or metoclopramide 20 mg plus placebo at 15 min intervals for up to three doses, or until pain relief occurred [105]. Pain intensity was recorded using a standard visual analog scale (VAS) at 0, 15, 30 and 45 min. Results were surprising in that although both groups experienced more that 50 mm improvement in the VAS score after treatment, the improvement was smaller in the magnesium group for the primary end point, which was the between-group difference in pain improvement when the initial and final VAS scores were compared. Results also favored the placebo group when comparing the proportion of patients with normal functional status at the final rating. The authors suggested that adding magnesium to metoclopramide might somehow diminish the efficacy of metoclopramide in decreasing migraine pain. The second emergency room study, also randomized, double-blind and placebo-controlled, compared the effectiveness of intravenous magnesium sulfate and intravenous metoclopramide with placebo [106]. Patients received either metoclopramide 10 mg, intravenous magnesium sulfate 2 g or normal saline, and then rated their pain using VAS scores at 0, 15 and 30 min. Subjects were subsequently followed up by telephone over the next 24 h to assess for headache recurrence. Each group showed more than a 25 mm improvement in the VAS score at 30 min, which was the study's primary end point. Nonetheless, there was no significant difference in the mean changes in VAS scores for pain, although the need for additional rescue medication was higher in the placebo group. Recurrence rates within 24 h were similar among the groups.

Treatment of cluster headache attacks

Intravenous magnesium may also be effective in the treatment of episodic cluster headache. One study, in which 22 cluster headache patients were treated with magnesium sulfate 1 g, showed that 41% reported 'meaningful relief' after treatment [107]. 'Meaningful relief' was defined as either a complete cessation of attacks or relief for more than 3 days.

Magnesium & menstrually related migraine

Magnesium deficiency may be particularly common in women with menstrually related migraine. A prospective study with 270 women, 61 of whom had menstrually related migraine, showed that the incidence of IMg^{2+} deficiency was 45% during menstrual attacks, 15% during nonmenstrual attacks, 14% during menstruation without a migraine and 15% between menstruations and between migraine attacks [108]. Although the serum ionized calcium (ICa^{2+}) levels were normal, the ICa^{2+}/IMg^{2+} ratios were elevated in menstrual migraine. Abraham and Lubran also reported that red blood cell magnesium deficiency might account for the symptoms of the premenstrual syndrome [109], which could include migraine [48]. These findings are consistent with the results of the clinical study by Facchinetti *et al.* (described previously, under 'Treatment with Oral Magnesium'), in which women with menstrual migraine reported a significant decrease in headache days, and an improvement in the Menstrual Distress Questionnaire Score, after receiving treatment with oral magnesium [48].

Pediatric migraine & magnesium

Pediatric migraine has also been linked to magnesium deficiency. A significant reduction in serum, red blood cell and mononuclear blood cell magnesium concentration has been noted in pediatric migraineurs (with and without aura) when compared with TTH patients and healthy controls [52,110]. Results from one of those studies also showed that the electromyographical (EMG) ischemic test was positive in 71% of migraine patients, but only in 9.5% of TTH patients [110], thus corroborating the role of magnesium not only in the pathogenesis of migraine but also for a condition of neuromuscular hyperexcitability, which includes muscle spasms, cramps, hyperventilation, asthenia and headache [111].

Magnesium supplementation may be a good option for preventative treatment of pediatric migraine, given its safety and tolerability. In a randomized, double-blind, placebo-controlled trial with children and adolescents aged 3–17 years, a statistically significant downward trend in headache frequency was noted in the magnesium oxide group but the slopes of the two lines were not statistically different from each other [112]. Therefore, it could not be definitively determined whether treatment was superior to placebo in preventing frequent migraine headache in this population.

Role of magnesium in other neurological disorders

Given magnesium's essential role in cellular functions, there has been speculation that alterations in magnesium levels in the setting of CNS insults might have an impact on neurological outcome. Some studies have shown that patients with low CSF or serum magnesium have worsened neurological outcomes after cerebral ischemia and traumatic brain injury [113–115], and others have indicated that alterations in free brain magnesium occurs after these insults [116–119]. Based on these studies, the possibility of magnesium's use as a form of neuroprotective treatment for traumatic brain injury, seizure, subarachnoid hemorrhage and cerebral ischemia has been hypothesized. However, the results of animal studies evaluating the neuroprotective effect of magnesium after brain insults have been variable, as reviewed by Meloni and Knuckey [120]. While five studies found a neuroprotective effect [121–125], two studies were negative [126,127] and two reported a positive outcome only when treatment with magnesium was combined with postischemia hypothermia [128,129]. Furthermore, the IMAGES acute stroke clinical trial found that magnesium administered within 12 h of the onset of an acute stroke with limb weakness was ineffective, in that no significant differences in mortality and disability were found between patients treated with intravenous magnesium or placebo [130]. The Field Administration of Stroke Therapy – Magnesium Phase 3 Clinical Trial (FAST-MAG), which is assessing the potential of early magnesium administration by paramedics in acute stroke treatment [131], showed encouraging clinical outcomes in a pilot study. The Phase III trial is currently underway [201].

Intravenous magnesium, as used in the treatment of preeclampsia, may also have a role in the prevention of cerebral palsy, a leading cause of chronic childhood disability [132]. This was initially observed in a 1995 case–control study [133], which showed that very-low-birth weight children with cerebral palsy were much less likely to have had *in utero* exposure to magnesium sulfate than control subjects, suggesting a protective effect of magnesium against cerebral palsy in this population. Very recently, a randomized, double-blind, placebo-controlled study with 2241 women at risk for delivering preterm infants showed that the children of those women who were given magnesium sulfate just before birth had a significantly lower rate of cerebral palsy compared with children of subjects who received placebo [134]. Women in the treatment group received a 6 g bolus of intravenous magnesium sulfate followed by an infusion of 2 g/h until delivery or for up to 12 h.

Expert commentary

Magnesium plays a vital role in a multitude of cellular and physiological processes, and its involvement in the pathogenesis of migraine has also been well-described. Although migraine attacks have been associated with magnesium deficiency, this is difficult to assess with routine blood testing. Treatment should therefore be considered in migraineurs based on clinical suspicion. Both oral and intravenous magnesium are simple, safe, inexpensive and well-tolerated, and may be particularly effective in certain subsets of migraine patients. We recommend daily treatment with 400 mg of chelated magnesium, magnesium oxide or slow-release magnesium in patients with symptoms suggestive of hypomagnesemia, such as migraine headaches, premenstrual syndrome, cold extremities and leg or foot muscle cramps. Some patients require and tolerate higher doses of oral magnesium, up to 1000 mg of magnesium oxide. Diarrhea and abdominal pain are common limiting factors for dose escalation. We use intravenous magnesium for acute treatment of migraine, where it can be effective in up to 50% of patients, and in those patients who do not tolerate, do not absorb or are unable to comply with oral magnesium supplementation. Some patients find great benefit from monthly (often premenstrual) prophylactic infusions of magnesium sulfate 1 g.

Five-year view

Over the next 5 years, we hope that large-scale, randomized, double-blind, placebo-controlled studies will be conducted to better characterize the efficacy of both oral and intravenous magnesium in preventive and acute migraine treatment. In addition, studies that evaluate the use of magnesium in combination with other acute headache treatments, such as aspirin, may also aid in the understanding of magnesium's effect on migraine attacks. Research on the use of magnesium for other indications can potentially decrease the morbidity associated with those neurological disorders and lend further insight into the effects of magnesium treatment. The early use of intravenous magnesium in acute stroke, as assessed in the ongoing FAST-MAG trial, may significantly improve the neurological outcome for those patients, and the perinatal administration of magnesium sulfate to women at risk of preterm delivery may decrease the rates of cerebral palsy in their children.

Financial & competing interests disclosure

Alexander Mauskop would like to state that he is the inventor of Migralex™, a combination of magnesium and aspirin. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Magnesium is an essential intracellular cation that plays a role in many facets of migraine biogenesis. Magnesium deficiency has been associated with the promotion of cortical spreading depression (CSD; via its interaction with the NMDA glutamate receptor), neurotransmitter release, platelet aggregation and vasoconstriction.
- Magnesium deficiency is common, but difficult to assess with routine laboratory testing since total serum levels do not reflect the true total body stores. Hypomagnesemia should therefore be suspected in patients with chronic illness, menstrually related headaches, cold extremities or leg and foot cramps, clinical symptoms such as apathy, depression, delirium, seizures, paresthesias, tremors or general weakness.
- Migraine attacks have been associated with low levels of magnesium in the brain, CSF and serum. Interictal studies of serum, plasma, and intracellular magnesium levels have yielded inconsistent results. True magnesium levels are best assessed with red-blood cell (RBC) magnesium, the magnesium load test or ionized magnesium (IMg^{2+}) levels.
- Regarding migraine prophylaxis with oral magnesium, two studies have shown a beneficial effect, and one recent study showed that supplementation with magnesium citrate resulted in a significant decrease in migraine attack frequency and severity when compared with pretreatment values. In patients in whom there is a clinical suspicion of magnesium deficiency, we recommend daily treatment with 400 mg of chelated magnesium, magnesium oxide or slow-release magnesium, as these formulations are likely to be the best absorbed. Diarrhea may be a limiting adverse effect in some patients.
- Although the data on the use of intravenous magnesium for the acute treatment of migraine is conflicting, it may be particularly beneficial for women with menstrually related migraine or patients with migraine with aura. The standard dose and formulation is magnesium sulfate 1 g.

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