Use of magnesium citrate in the prophylaxis of vestibular migraine in childhood

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Abstract Magnesium is involved in protein synthesis, muscle contraction, cardiac excitability, glycolysis, hormonal synthesis and in the production of at least 300 human enzymes.
In this case, enzymes with an energetic function are involved and the presence of magnesium in the enzymes responsible for anaerobic glycolysis is a confirmation of this. ATP synthetase has magnesium as a cofactor. And the same is true for ATP stabilization systems, which therefore always acts as an ATP-Magnesium complex. The Magnesium-ATP complex governs all the "membrane pumps" (such as the Sodium / Potassium and Calcium pumps) of our organism. Magnesium deficiency plays an important role in the pathogenesis of migraine, both in adults and in children, promoting "cortical spreading depression". The authors studied a sample of 15 children affected by vestibular migraine who were treated with magnesium citrate, concluding that magnesium could represent a valid aid, without side effects, for the therapy of vestibular migraine even in childhood.

Keywords:Magnesium, Magnesium citrate, Vestibular migraine, Glutamate, GABA, Sodium / Potassium pump, Resting membrane potential.

Magnesium is a metal positioned at number 12 on the periodic table of the elements and, like iron, is an essential mineral.

It takes its name from the Greek word (Μαγνησία, Maghnesía) which indicates a prefecture of Thessaly in ancient Greece called Magnesia.

In biology and in particular in the study of the origin of life, including extraterrestrial ones, magnesium (Mg) is recognized as having an important function in evaluating the presence of those primordial forms that are about to make the leap from organic molecules to life-bearing molecules (Kean S, 2010).

The deposits of magnesium on the earth's crust demonstrate the presence of water and therefore are indicators of possible life. The magnesium compounds lower the freezing point of the water which, under the ice, remains liquid even at low temperatures.

Complex organisms use iron (as in hemoglobin) to transport and store energy, but primordial forms of life, such as cyanobacteria, use magnesium to achieve the same purpose (S. Kean, 2010). The most important organic substance on earth, chlorophyll (given that photosynthesis and our respiration depend on it), contains a magnesium atom (Gerola, 1998). A yellowing leaf is often a sign of magnesium deficiency.

In the human body, magnesium is the second most represented cation (after potassium).

The recommended daily intake of magnesium for an adult is 350 mg for men and 300 mg for women (Lichton, 1989), which can be increased up to 450 mg during pregnancy and breastfeeding.

Regarding children (Lichton 1989) there are no certain parameters on their needs. However, we point out that the dietary doses recommended as established by the Food and Nutrition Council of the National Research Council, expressed in mg / day, are 150 mg for children aged 1-3 years; for the age group 4-6 years 200 mg; 7-10 years 350 mg.

Magnesium can be taken from many food products, such as cereals (especially whole grains), walnuts (160 mg per 100 grams of product), almonds (200 mg), peanuts (120 mg), millet and buckwheat (120 ÷ 140 mg), cocoa (400 mg), wheat germ, lentils, green vegetables (especially spinach) and also in meats, starchy foods and dairy products. Finally, there are mineral waters rich in magnesium salts called magnesium waters (Fidanza, 1998).

The absorption of magnesium occurs in the small intestine. Only the unabsorbed food portion is excreted with the faeces, given that the Mg produced by the bile and pancreatic and intestinal juices is totally reabsorbed. Most of the reabsorbed magnesium is eliminated by the kidney (Fidanza,1998).

The human body usually contains 21-28 total grams of magnesium, 99% of which is located in the bones, muscles and soft tissues and only 0.3% is contained in the serum. (Jahnen-Dechent, 2012) Therefore, performing magnesemia, for diagnostic purposes, assumes a completely relative value.

The concentration of magnesium available in the body depends on maintaining a dynamic balance between the reserves present in the bone, absorption in the intestine and excretion in the kidney.

This balance is of fundamental importance for the health of the human being since magnesium regulates the kinetics of ion transport across membranes, the synthesis of nucleic acids and proteins, neuromuscular transmission and energy metabolism. (Gerry, 2017)

To mention the most important processes, magnesium is involved in protein synthesis, muscle contraction, cardiac excitability, glycolysis, hormonal synthesis and in the production of at least 300 human enzymes.

In this case, enzymes with an energetic function are involved and the presence of magnesium in the enzymes responsible for anaerobic glycolysis is a confirmation of this.

The same is true for some enzymes of the Krebs cycle and for those of oxidative phosphorylation. ATP synthetase has magnesium as a cofactor. And the same applies to ATP stabilization systems which act as an ATP-Magnesium complex.

The Magnesium-ATP complex governs all the “membrane pumps” (such as the Sodium / Potassium and Calcium pumps) of our body which, to carry out their work, require energy and therefore ATP and magnesium, basic elements for the functioning of the Central Nervous System (CNS) (Xue, 2019).

In cases of Magnesium deficiency, the consequent altered functionality of the membrane pumps reduces the resting membrane potential of the nerve cell with a consequent condition of hyperexcitability. The symptoms in these cases will be characterized by cramps, migraines, headaches, dysmenorrhea.

It is known (Bear, 2012) that the most powerful excitatory neurotransmitter of our Central Nervous System, glutamate, has three receptor subtypes: NMDA, AMPA and Kainate.

Given that little is known about the function of Kainate receptors, we focus our attention on AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid) and NMDA (N-methyl-D-aspartic acid) receptors.

The AMPA channels are permeable to Na + and K + but not to Ca ++: the AMPA receptors therefore facilitate the entry of sodium ions into the cell causing depolarization.

NMDA receptors, on the other hand, are permeable to Ca ++ and have voltage-dependent activity. At the post-synaptic level, the calcium ion is able to activate enzymes, regulate the activity of numerous channels and influence gene expression. But the exaggerated activity of the NMDA receptor, resulting in a massive entry of calcium ions into the cell, can cause neuronal death due to excitotoxicity.

This is where the Magnesium ion (Mg ++) and its blocking function (Bear, 2012) come into play. When the membrane potential is at rest, the magnesium ions prevent the passage of other ions into the nerve cell. Magnesium ions get out of the pore only when the membrane is depolarized, generally after the activation of the AMPA receptors (Bear, 2012).

Whenever the neurons are unable to generate sufficient ATP (as in migraine), to keep the ion pumps running, the membrane depolarises, the Mg ++ ions leave the pore and vice versa the Ca ++ ions enter and their entry causes the synaptic release of glutamate.

Glutamate depolarizes neurons, increases the concentration of intracellular Ca ++, which causes the release of a greater amount of glutamate.

A vicious circle is created, for which glutamate reaches high concentrations, overexciting neurons to the point of causing their death through the aforementioned process called glutamate “excitotoxicity”.

This phenomenon also generates toxic quantities of nitric oxide and free radicals that compromise neuronal function (Pierangeli, 2015; Edelstein, 2009).

Until now we have focused our attention on the excitatory neurotransmitter glutamate. But hyper-excitation can also be a consequence of a lack of inhibition and here the most powerful inhibitor of the central nervous system comes into play, which is gamma amino butyric acid or GABA. As absurd as it may seem, the most powerful inhibitor of the CNS, GABA, is formed, by the action of glutamate decarboxylase, directly from the most powerful exciter of the CNS, Glutamate. The glutamate decarboxylase enzyme acts correctly if it finds, as a substrate, vitamin B6 and, once again, magnesium (Revue, 2007).

14.5% of the population suffers from hypomagnesemia and migraine sufferers often develop hypomagnesemia (Pierangeli, 2015) due to low nutritional intake, genetic inability to absorb magnesium, renal atrophy and excessive excretion from stress, alcoholism and uremic states.

Iatrogenic hypomagnesemia from lithium or proton pump inhibitors has been described (Liao, 2019),

Studies (Mauskop, 2012) show low plasma levels of magnesium during migraine, such as to determine a reduction in the threshold of Cortical Spreading Depression (CSD) of migraine sufferers.

Therefore, (Mauskop, 2012) magnesium can block glutamate-dependent CSD, regulate NMDA-dependent pain transmission, and regulate cerebral blood flow.

Ultimately, hyperexcitability and CSD are a consequence of biochemical phenomena due to the alteration of energy metabolism and ATP, ion channels and glutamate but also, if not above all, of magnesium metabolism.

From these premises, in order to restore the resting membrane potential that is at the origin of the hyperexcitability and excitotoxicity of glutamate, an hypothesis was also made about the possible use of magnesium in the prophylaxis of migraine (Pringsheim T, 2012).

This indication appears even more meaningful in pregnant women (Allais, 2015), where prophylaxis with magnesium and vitamins of the B complex proves effective and in the absence of any kind of risk.

This indication appears even more meaningful in pregnant women (Allais, 2015), where prophylaxis with magnesium and vitamins of the B complex proves effective and in the absence of any kind of risk.

As the multifaceted role of this ion in migraine, the use of magnesium in the treatment of vestibular migraine, both in the acute phases and for preventive purposes, has given results that have made it possible to consider it a simple, economical, safe and well tolerated (Levi, 2014; Teigen, 2015; AA.VV, 2012).

In assessing the reliability of publications on the subject, it should be noted that the magnesium blood concentration dosage is an unreliable test, because most of the magnesium is contained within the cells and only 0.3% is present in the serum (Jahnen-Dechent W, 2012).

A correct dosage of this ion should therefore be performed inside the leukocytes and granulocytes or with the “Magnesium load curve” and its subsequent detection in the faeces and urine or, finally, but only in a few centers, with mass spectrometry on the hair.

Pharmacology offers us different formulations of Magnesium Salts. Among these, the least expensive are the oxide salts or magnesium carbonate which, being low molecular weight, have extremely low costs. But these have a low percentage of intestinal absorption (bioavailability), since they are not very soluble, they adhere to the intestinal parts and easily form complexes with the mucus. Ultimately, their absorption is estimated at 4% of the ingested quantity. Another salt, magnesium chloride, has a high absorption value but a bitter taste and a high molecular weight. Therefore, due to its aftertaste similar to sea water, it is not appreciated by patients. For this reason we have turned to the marketing of a large family: organic magnesium salts. This includes highly absorbed molecules: magnesium pidolate, magnesium citrate, magnesium lactate and magnesium aspartate (Zaroddu, 2019).

Magnesium citrate is a salt consisting of the union of a magnesium atom and a molecule of citric acid. This formulation guarantees not only a greater intestinal absorption of magnesium (Walker A, 40) and therefore a high bioavailability but also an increase in the pool of circulating bicarbonates (magnesium bicarbonate), a facilitation of lactate drainage and a facilitation of energy metabolism. (Street, 2005).

This means improving the energy metabolism of ATP as this process (anareobic glycolysis with the production of lactates) is acid-forming (Street, 2005).

Other drug products contain citric acid mixed with magnesium carbonate. These two ingredients, once put in contact with water, react to form magnesium citrate and carbon dioxide which gives the product a pleasant effervescence. The citrate which, when ingested and metabolized, becomes magnesium bicarbonate, buffers this process and guarantees a longer duration to the energy process. Magnesium citrate is therefore made up of two synergistic components, since both the alkalinization due to bicarbonates and the magnesium itself improve the ATP balance.

The pharmacological association of Magnesium with Potassium is aimed at determining up-regulation of the Na + / K + membrane pumps. (Dorup, 1996; Sriboonlue, 2004)

Potassium should be taken with the diet in an amount of 2000 mg / day, a dose that should not be exceeded to avoid hyperkalaemia. Why associate Potassium with Magnesium? Because with Magnesium we restore energy to the cellular pump systems and among these to the Sodium / Potassium pump.

However, it is very obvious that, if this was primarily malfunctioning, the reuptake of the potassium leaked from the cell will not be observed and, on the contrary, the expulsion of sodium will not be observed. We are faced with a cell that loses potassium and retains sodium. These factors hinder the maintenance and restoration of the correct resting membrane potential. Therefore, it is necessary to give energy to the membrane pumps by administering Magnesium which facilitates the production of ATP and at the same time Potassium to supply the ions necessary for depolarization. The end is always the same to physiologically restore the resting membrane potential, thus eliminating cellular hyperexcitability.

- Hypomagnesemia and Down Beat Nystagmus in adults

As in the remaining components of the CNS, the otoneurological structures also seem to be affected by the condition of hypomagnesemia.

Recently (Comacchio, 2015) a case of primary down beat nystagmus (PDBN) due to hypomagnesemia was reported. PDBN ny is characterized by slow ocular drifts upward and rapid downward phases and is the most common form of acquired eye movement not inhibited by fixation. PDBN is essentially due to injury to the craniocervical junction or diseases of the lower brain stem and cerebellum. Cases of lithium or antiepileptic drug intoxication, abuse of toluene and metabolic disturbances such as vitamin B1 and B12 deficiency have also been reported. Hypomagnesaemia has rarely been reported as another possible cause of PDBN. Comacchio et al report a case of reversible high intensity PDBN, due to severe hypomagnesaemia with ataxia, objective vertigo and oscillopsia, with normal cerebellar MRI study.

- Migraine and neurological symptoms: Vestibular Migraine

Although common migraines are characterized (and not always) by the presence of headache, vestibular migraine is characterized by the presence of dizziness. Migraine is a disease, headache is a symptom, which is not always present in migraine sufferers.

Among the otoneurological symptoms of migraine we find vertigo (vestibular migraine) and / or paroxysmal torticollis (otolithic vestibular migraine).

The diagnostic criteria of vestibular migraine are now well established (Neuhauser, 2004) and there is no need to dwell on the subject here. It will be sufficient to remember that in migraine the pain persists between 2 and 72 hours and has at least two of the following four characteristics: it must have unilateral localization, it must be of the pulsating type, it must have medium or strong intensity and it is aggravated by physical activities of routines such as walking or climbing stairs. At least one of these symptoms is usually present: nausea or vomiting, photophobia and phonophobia.

Vestibular migraine is one of the first causes of dizzying symptoms in adults.

Magnesium (Sun-Edelstein, 2009) plays an important role in the pathogenesis of migraine by promoting “cortical spreading depression”. Magnesium deficiency is believed to affect the sensitivity of the glutamate N-methyl-D-aspartate (NMDA) receptor and cause, by excitotoxicity, the production of toxic quantities of nitric oxide radicals with consequent spread of cortical spreading depression (CSD) (Sun Edelstein, 2009).

- Infantile vertigo as a migraine equivalent

The International Classification of Headache Disorders 3rd edition ICHD 3, the third classification of episodic syndromes that can be associated with migraine, includes (in point 1.6) the benign paroxysmal vertigo of childhood and describes the diagnostic criteria. Periodic childhood syndromes, which can be classified as “pediatric migraine equivalents”, are a symptomatology that affects patients with a greater likelihood of developing migraines (with or without aura) in young adulthood. The equivalents are obviously not migraine precursors, since the pathology is already underway (Pagnini, 2003).

The International Classification of Headache Disorders III Edition (ICHD IIIb) 2013 also includes, among the periodic syndromes, cyclic vomiting, abdominal migraine, benign paroxysmal vertigo and benign paroxysmal torticollis.

The diagnosis (ICHD III b) is directed by the observation, in the absence of other otological, neurological and electroencephalographic manifestations, of at least five episodes of vertigo, sometimes accompanied by headache and which resolves spontaneously within minutes or hours. The migraine habitus is predominantly familiar (Baloh, 2002).

In pediatric patients, daily activities, such as physical, psychosocial, and school activities, could be significantly affected by migraines. This is mainly because vertigo can arise at any time and without warning symptoms.

Measurement of migraine-related disability, quality of life along with patient-reported outcome assessments have become a standard method over the past two decades, providing further information on how children perceive their altered health conditions and how these interfere with their daily activities. The doctor has to mediate between a pathology that is not actually worrying and a family environment very worried about the symptoms.

This mediation will necessarily have to be resolved with a therapeutic approach in which, in most cases, the doctor would like to avoid the prescription of drugs acting on the S.N.C. (Patniyot, 2016; Cuvellier, 2008)

Management of pediatric migraine includes acute treatment and prophylactic therapy.

- Acute treatment is based on the use of analgesics, such as paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs), as well as specific therapies for migraine such as triptans, while dopamine receptor antagonists are generally used in emergency settings.
- The goal of prophylactic therapy is to reduce the frequency and severity of migraine attacks and frequently used drugs are beta-blockers, calcium channel antagonists, antiepileptic drugs, antidepressants and antihistamines which are not always indicated and may also have side effects (Bellini, 2013).

With these premises, the use of a natural substance for migraine prophylaxis was proposed: magnesium (Levi Teigen, 2015). Several studies (Mauskop, 2009; Hsiao-Yean Chiu, 2016; E. Köseoglu, 2008; Sun-Edelstein, 2009;

Mauskop, 2009) evaluating oral magnesium supplement for migraine prevention have reported a significant reduction in migraine frequency and severity.

According to American Academy of Neurology and American Headache Society guidelines, Magnesium is likely effective for migraine prophylaxis based on level B evidence.

In addition, in the guidelines of the Canadian Headache Society, magnesium citrate is strongly recommended for migraine prophylaxis (Pringsheim, 2012).

Other authors also report a reduction in autonomic symptoms in pediatric patients (Kovacevic, 2018).

With these premises, we conducted a study in order to evaluate the impact of magnesium in the treatment of migraine in a group of pediatric patients.

Personal research

The aim of our study was to evaluate the effectiveness of magnesium citrate therapy in reducing symptoms in pediatric patients diagnosed with vestibular migraine.

The study involved 15 patients (8 females and 7 males) aged 5-15 years (mean age 10 years).

The 15 patients came to our attention with different symptomatological clusters:

- Episodes of headache and vertigo in 8 patients and, in 3 of these, associated vomiting.
- Kinetosis and imbalance in 3 patients.
- Headache, vertigo, phonophobia and spontaneous nystagmus in 2 patients
- Frequent episodes of imbalance, migraine with aura and fullness headset in 1 patient
- Appearance of “rustling” tinnitus, headache, confusional state e stiff neck in 1 patient.

The first step towards recognizing the nature of the pathological process responsible for the symptoms was a careful medical history conducted with the precious collaboration of parents, especially in patients under the age of 8.

Parents of patients frequently tend to underestimate the history of migraines because they believe that there is no correlation between symptoms and migraines. In this perspective, the use of drawing is of fundamental importance (Messina, 2011). Vertigo is a difficult symptom to describe, even for adults. The vertigo phenomenon itself is a symptomatic bodily expression and, at the same time, an intense psychic experience. Thus, when the vertiginous symptom is experienced, the different body sensations - from that of movement, to rotation, to instability - are accompanied by disturbing emotions. Feeling in motion, in “unstable equilibrium”, the feeling that “everything is spinning” or that the head is shaking from side to side, the feeling of being on the verge of falling, not standing up, or even the sensation of disarray: these are psychic experiences but also bodily, existential but also somatic, symbolic but also concrete (Messina, 2011). By inviting the child not to express his pathological condition in words but to draw it, representations are obtained that almost coincide with reality.

In the case of anamnesis, it is very important to assess familiarity: migraine is very frequent in the families of the children observed and in our sample we highlighted a familiarity for migraine in 6 cases.

In addition to the study of familiarity, it is essential not to stop only at the most common symptom of migraine (headache, which is found in 73% of our sample), but it is necessary to expand clinical research by investigating the appearance of dizziness (53% of patients) and imbalance (33% of patients) and episodic clinical manifestations preceding migraine defined in fact as migraine precursors; gastrointestinal disorders such as nausea (26.6% of the sample) and vomiting (20% of the sample), kinetosis (46.6% of the sample) belong to this category of manifestations.

A migraine equivalent, benign paroxysmal torticollis, was present in only one patient of the sample.

Additional conditions that can occur in children with Vestibular Migraine include sleep disturbances (20% of patients) and bruxism (20% of patients).

By evaluating the auditory symptoms it can be seen that, compared to the total sample, only one patient has tinnitus and another patient has fullness that is accentuated with vertigo.

Following the medical history, the patients underwent the following diagnostic procedure (Balzanelli, 2021):

- Liminal tonal audiometry
- Otoscopy
- Impedance measurement
- Researchofspontaneousnystagmusinvideo-nystagmoscopy
- Search for positioning nystagmus (using the maneuvers
- by Pagnini-McClure and Dix-Hallpike and by Semont)
- Head Shaking Test (HST)
- Vibration test
- Romberg test
- Mingazzini test
- Postural evaluation
- Evaluation with a stabilometric platform
- ATM evaluation
- Video head impulse test (vHIT)

In some cases, an in-depth diagnostic was performed using tests: cervical and ocular VEMPs, ABR.

Furthermore, in patients aged between 5 and 13 years, we asked to create a drawing that represented the perceived disturbance, the dizzying sensation experienced by the child. The children with Vestibular Migraine produce drawings that indicate their disorder, with closed, concentric, spiral or scribble lines.

The data collected through the medical history, physical examination and diagnostic investigations made it possible to diagnose vestibular migraine using the 2013 ICHD-3 BETA criteria.

Within our case series we have identified, based on the intensity of the symptoms, three groups of patients:

GROUP A - Severe symptoms (3 patients)

GROUP B - Moderate symptoms (3 patients)

GROUP C - Mild symptoms (9 patients)

All patients received, for a period of six months, a sachet / day per os of a food supplement containing 200 mg of Magnesium, in the form of Magnesium citrate, and 350 mg of Potassium in the form of Potassium citrate.

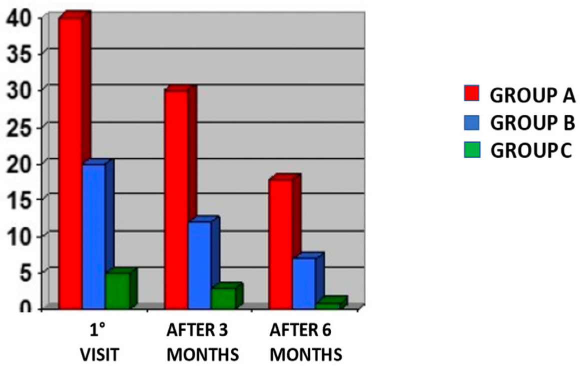
Since a pediatric dosage of the product is not commercially available, it was necessary on the one hand to obtain informed consent and on the other hand to subdivide the dosage into several administrations.

Results

We found excellent compliance with the therapy, also favored by the relationship of trust created in the treatment process with children and their parents. No child complained of iatrogenic gastrointestinal disorders, even if expected.

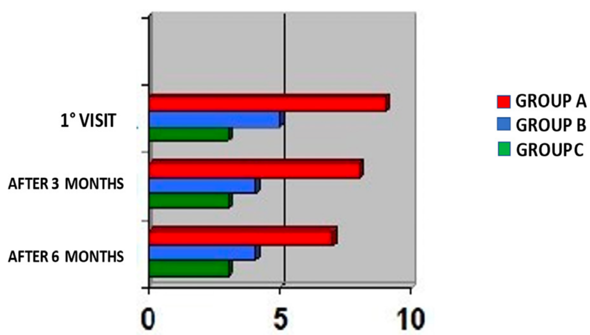
At check-ups, carried out after 3 months and after 6 months of treatment, we assessed the gradual reduction of symptoms through physical examination, vestibular tests and an interview with patients and their parents. We have paid particular attention to four aspects:

1. Frequency of migraine attacks and headache, assessed by the number of episodes occurring monthly (Graph 1)



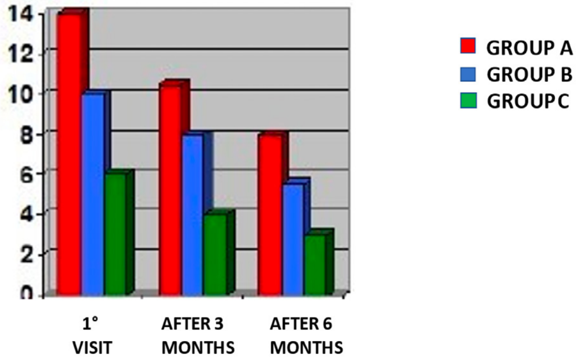
Graph 1. Frequency of migraine attacks and headache

2. Intensity of migraine attacks assessed by NRS (numerical rating scale)



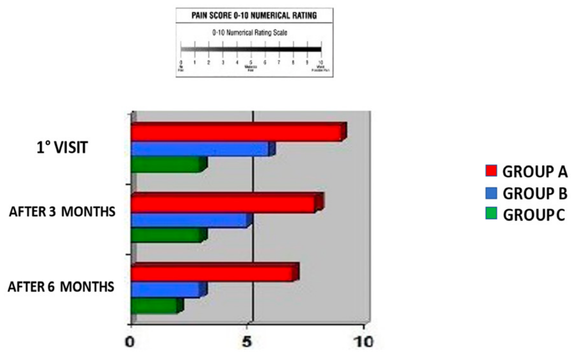
Graph 2. Intensity of migraine attacks and of headache

3. Episodes of imbalance and vertigo, evaluated by the number of phenomena of imbalance and / or instability and / or vertigo occurring monthly (Graph 3)



Graph 3. Frequency of episodes of imbalance and vertigo

4. Intensity of the vertiginous symptom assessed by NRS (numerical rating scale) (Graph 4)



Graph 4. Intensity of the vertiginous symptom assessed by NRS (numerical rating scale)

Furthermore, during the observation period:

- 7 patients reported a reduction in the intensity of migraine attacks.
- In most cases there was a reduction in school absences caused by symptoms related to the disease.
- Parents reported having observed in their children a gradual improvement of mood and participation in activities, an important aspect that we ourselves found at checkups.
- Only one patient did not return to the follow-up visit after 6 months.

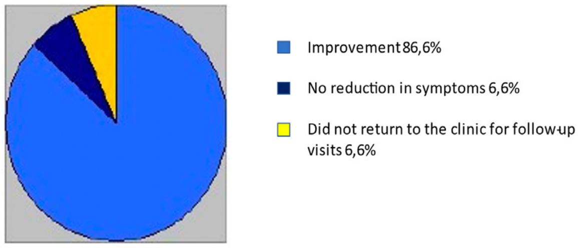
At the end of the study, for an overall evaluation of the path taken together with the children with vestibular migraine, we asked them to express an opinion on the improvement of their state of health.

We thus obtained the following results:

- 13 patients expressed an overall improvement, mainly due to a reduction in the frequency of onset of symptoms.

- 1 patient expressed no reduction in symptoms.

- 1 patient did not return to the clinic for follow-up visits



Graph 5.

Conclusions

The treatment of 15 pediatric patients, diagnosed with vestibular migraine, with 200 mg per day of magnesium, in the form of magnesium citrate, resulted in a significant reduction in the frequency and intensity of migraine attacks, dizziness and imbalance.

Being critical, we wish to point out that:

1. The observational period should be protracted over time since it is very obvious that otoneurological crises have a variable course.
2. The statistical sample must be expanded to obtain statistically appreciable data.

Nevertheless, on the basis of our personal experience and in the light of the satisfactory results obtained, we believe we can conclude, in accordance with the results reported in the bibliography, that magnesium, even more so if in the form of citrate, could represent not only a valid aid for vestibular migraine therapy even in childhood but above all a treatment without side effects.

Future hypotheses

There is a correlation between childhood migraine equivalent and Menière's disease and in this context, also due to the important premises made, we could propose the use of magnesium as an adjuvant to therapy in Menière's disease.

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