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Role of magnesium in headache pathogenesis in children and adolescents

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Article is dedicated to the problem of headache in children. This pathology is being found more frequently in pediatric and children's neurologic practice. The authors examine headache pathogenesis from the position of magnesium deficiency. Analysis of results of the modern studies on magnesium deficiency and its correction in patients with headache indicates that magnesium metabolism may play an important role both in pathogenesis of different headache types and in its treatment and prevention.

Keywords: *headache, tension headache, migraine, cluster headache, primary headache, children, adolescents, magnesium deficiency, NMDA-receptors, magnesium pidolate, magnesium citrate, pyridoxine.*

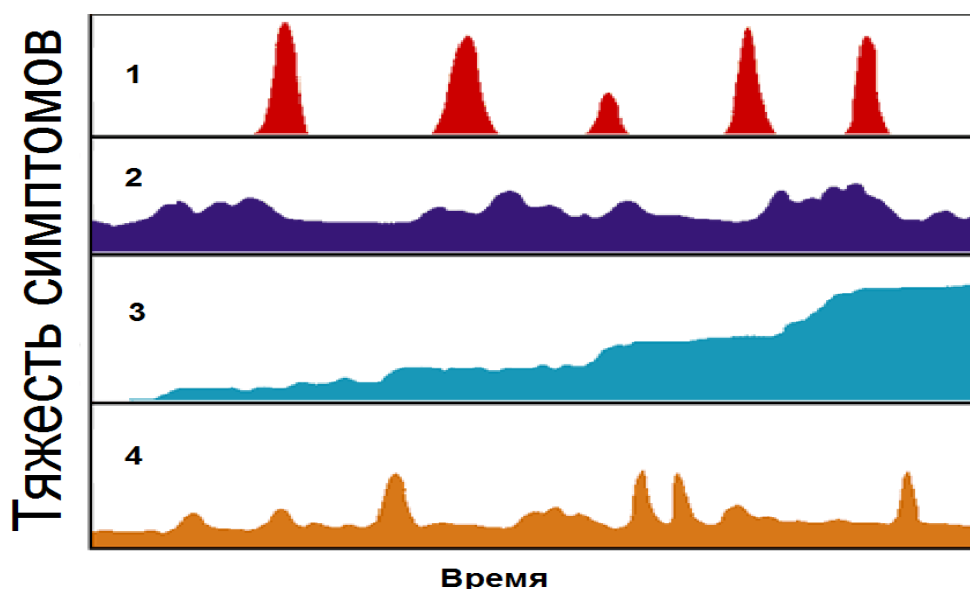
HEADACHE: clinical features, risk factors and diagnostics

Headache is a frequent cause of health care encounters, and the frequency adds up with age. Children as well as adults may experience primary and secondary headaches, of which the most frequent primary forms are migraine, tension headache, cluster headache, and chronic daily headache (CDH). In some cases, headaches in children may be caused by infections, stresses, high-level anxiety, or head injuries. It is of importance to pay attention to headache, especially if new symptoms appear, or if the ache becomes stronger or more frequent.

Acute headache may be secondary to a systemic infection, such as influenza, pneumonia, sepsis; a local inflammation, such as sinusitis, dental caries or otitis media; a head injury, meningitis (characterized by impaired consciousness with photophobia and rigidity of occipital muscles); and subarachnoid hemorrhage, which begins suddenly and features a severe occiput pain, possible consciousness impairments, and rigidity of occipital muscles. Periodically recurrent headaches are most frequently migraines with aura, nausea, emesis, pallor, and burdened family history; tension headaches involving head and neck muscles and usually suffered at the end of the day; neurosis headaches, which are difficult to clinically differentiate from tension

headaches; headaches caused by increased intracranial pressure (usually occur in the morning and are accompanied by emesis; they become severer when the person coughs or sneezes, and progress if personal behavioral changes or focal neurological deficits arise or intensify). Causes of repetitive headaches also include benign intracranial hypertension, systemic arterial hypertension, uremia, occasional hypoglycemia, repetitive epileptic seizures, lead or carbon monoxide intoxication. **Pic. 1** depicts patterns of the most frequent headaches in children and adolescents.

Pic. 1. Headaches in children and adolescents. 1 – acute periodic headache: classic or associated migraine; 2 – chronic non-progressive headache, i.e. tension headache or anxiety/depression/somatization-accompanying headache; 3 – chronic progressive headache: swelling, benign intracranial hypertension, cerebral abscess, hydrocephalus; 4 – acute chronic headache of non-infectious etiology: tension headache episodes in a migrained patient.



Тяжесть симптомов *Symptom severity*
Время *Time*

In general, headache symptoms in children may be categorized according to the International classification of head disorders, ICHD-II-2004, as in the general population.

Migraine. Pulsating or "throbbing" pain accompanied by nausea, emesis, phonophobia, and abdominal pain. Even post-natal infants can experience migraine. Like adults, children can experience a ≥ 1 hour-long migraine. As a person ages, symptoms change. Toddlers are not able to convey what is wrong; instead, they cry and hold their head in the hands to express the pain. A nurse can notice the child's pallor and decreased activity. An older child may not only cry, but also tilt when sitting or walking forwards and backwards, have disordered movement coordination or emesis. As a rule, migraine in children occurs at the end of the day. At such an

age, headache episodes usually lasts an hour or two and may affect one or both sides of the head. However, it must not be ignored that infants are often not able to localize their aches correctly and may mention "abdominal pain", for instance. There also exists the abdominal migraine diagnosed in children with stereotypical recurrent ache episodes in the umbilical region. It is very important to rule out somatic pathology and carry out additional tests if required. In adolescents, migraine sets on gradually and intensifies over several minutes or hours. Migraine may become stronger when a person moves his/her head, sneezes or strains. Non-stop movement, physical exertion, and bright light may also amplify the pain. Headache may last up to 72 hours. In children, migraine is often accompanied by syncope, abdominal pain, and kinesis. Some migraine-affected children experience visual aura several minutes before the headache sets on. Aura may be perceived in the form of zigzag-shaped lines, bright spots, or may even result in a temporary partial sight loss.

Tension headache as a rule features the following: pain in pericranial muscles on both sides on palpation; dull non-pulsating moderate pain; pain not amplified by moderate physical exercise; not accompanied by nausea or emesis. In younger children, refusal to play games and sleepiness may also be tension headache symptoms. Tension headache may last from 30 minutes to several days.

Cluster headaches are rare in under-10 children. It is usually a group of five or more headache episodes (i.e. a cluster) that emerges one to eight times a day. Stabbing and acute unilateral pain may last from 15 minutes to 3 hours. It is accompanied by lachrymation, rhinorrhea, anxiety, and agitation. Boys suffer from it more frequently.

CDH. Migraine and tension headache frequency may have an upward trend. If headaches occur in more than 15 days a month over more than 3 months, CDH is diagnosed. Sometimes, infections and mild head injuries may manifest themselves in the form of persistent headaches. CDH may also result from overintake of painkillers, including over-the-counter drugs.

Although the same types of headaches are registered in children as in adults, symptoms are often different. For instance, migraine in adults is almost always unilateral. At the same time, migraine in children is often bilateral. Besides, headache symptoms in children do not always correspond to the headache classification criteria. As a result, it is difficult to define what type of headache is present, especially in younger children, who are not able to describe their symptoms correctly. Headaches in children may be related to head or neck injury, vascular disorders of the cranium and cervical vertebrae, non-vascular intracranial disorders, infections, homeostasis disorders, cranial structure pathologies, and psychological disturbances, which are highly comorbid with any headache [1].

Serious stress and anxiety caused by social conflicts with peers, teachers, or parents, home task overload and excessive fascination with IT products (computers and gadgets) are negative headache-related factors. When depressed, children may start complaining about the headache, especially if lonely or melancholic. DNA is also an important migraine factor. According to our monitoring, neurotic and anxiety disorders manifest themselves with a set of somatovegetative complaints forming the so-called vegetative dystonia in 10-17-year-old children. Besides the headache, 100% of pediatric patients experience increased fatigability, 83% feature hyperventilation syndrome symptoms; sleep disorders, cardiovascular and digestive tract manifestations are also present [2].

It is known that some nitrate- and glutamate-containing foods and drinks, i.e. fast food, sausages, bacon, etc., as well as excessive amounts of caffeine in chocolate, coffee, tea, and coke-based drinks, do provoke headaches by disrupting intracellular balance of essential microelements, especially of magnesium and calcium [3].

Although in most children the headache prognosis is positive, thorough clinical attention (red flags) shall be given to the headaches occurring once a week or more often, if the symptoms have emerged or amplified after a head injury and if the pain is accompanied by emesis, sight and coordination disorders, dizziness, body temperature increase, neckaches, and rigidity of occipital muscles.

Usually, appropriate use of drugs, including analgesics, and non-medicinal treatment, such as family (entourage) and child's lifestyle changes, alleviate headaches.

To treat headache in a child successfully, it is necessary to define its cause. It is important to analyze the history of the disease, reveal the possible triggers and subsequently correct behavior or lifestyle. Headache Log, where frequency and intensity of pain are registered, is very informative to analyze (Appendix 1). Physical checkup involves measuring height, body weight, head circumference, arterial pressure and heart rate, inspecting eyes, neck, head, shoulders and the spinal column. Neurological checkup is intended to assess locomotor, coordination, and sensory functions. In some cases, additional tests are required for accurate diagnosis or ruling out other headache-provoking diseases, such as computed tomography, which helps to diagnose swelling, infections, and other pathologies; magnetic resonance tomography also helps to identify swelling, CVA, or aneurisms, and also to investigate the blood vessels supplying the brain. Cerebrospinal puncture helps to diagnose bacterial or viral meningitis.

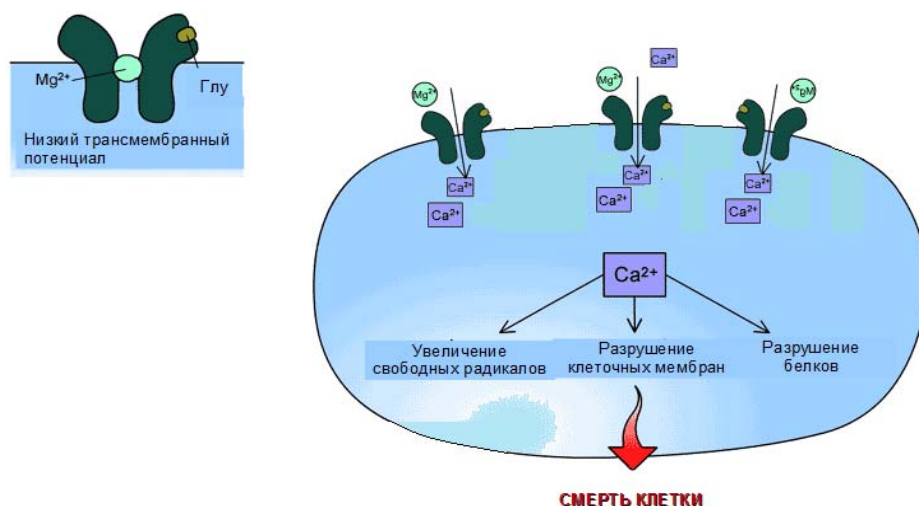
Headache may develop in any child; however, but risk groups have been identified. They are most frequent in puberty-aged girls and in children with a family history of headaches, especially of migraines. Recently, magnesium deficiency has been identified as a primary headache factor and pathological basis. Based on the results of long-term studies in Russia and abroad, it has

been proven that magnesium ions Mg^{2+} control the function of the voltage-gated membrane ion channel for Ca^{2+} , Na^{+} , K^{+} and are universal natural stabilizers (antagonists) for all subtypes of NMDA-receptors — ionotropic glutamate receptors that selectively link NMDA (N-methyl-D-aspartate) — and thus are crucial for pain syndrome formation and chronization [3-4].

PATHOGENETIC ROLE OF MAGNESIUM

Mg^{2+} blocks ionic channels of the NMDA receptors and thus prevents excessive leakage of Ca^{2+} into cells; this prevents excitotoxicity development (pic. 2). Mg^{2+} reduction in the brain and/or peripheral nerves identified in people with headache leads to a Ca^{2+}/Mg^{2+} ratio increase, and consequently to hyperexcitability of cells and tissue [5]. When Mg^{2+} is deficient, glutamate receptors are stimulated, the flow of Ca^{2+} ions into neurons increases, and excitotoxicity may develop (see pic. 1) [6-7]. Cellular Mg^{2+} deficiency also activates the Ca^{2+} -dependent inflammatory cascade with uncontrollable production of the P substance and nitrogen oxide (II) which leads to cerebrovascular spasms, thrombocyte aggregation increase, intensification of the vasoactive action of serotonin, and weakens the impact of the prostacyclin-mediated relaxation of the soft vascular muscles [4, 8]

Pic. 2. NMDA receptor, Mg^{2+} , Ca^{2+} interaction pattern.
<http://www.stanford.edu/group/hopes/cgi-bin/wordpress/2011/06/about-glutamate-toxicity/> [9].



<i>Низкий трансмембранный потенциал</i>	<i>Low transmembrane potential</i>
<i>Глу</i>	<i>Glutamic acid</i>
<i>Увеличение свободных радикалов</i>	<i>Free radical increase</i>
<i>Разрушение клеточных мембран</i>	<i>Cell membrane degradation</i>
<i>Разрушение белков</i>	<i>Protein degradation</i>
<i>Смерть клетки</i>	<i>Cell death</i>

This enables us to discuss the role of magnesium deficiency as a ground for primary headaches pathogenesis, i.e. tension headache, migraine, cluster headache, via central and peripheral sensitization. According to clinical data, more than a half of headache patients are magnesium-deficient. The magnesium content in the monocytes, erythrocytes, and thrombocytes of headache patients is 40-50% lower [10-11]. The routine blood tests used to define the magnesium concentration in blood serum cannot serve as a true indicator of the tissue magnesium status, as the magnesium concentration in blood plasma accompanies a significant level decrease in the magnesium repositories. For this reason, standardized questionnaires are used alongside the laboratory tests for reliable magnesium deficiency diagnosis in different categories of patients.

Besides, a quick Mg^{2+} concentration drop in blood plasma and significant increase in the Ca^{2+}/Mg^{2+} ratio thereby are noticed in patients with frequent secondary headaches that occur after a mild or moderate head injury [12].

Magnesium deficiency also induces development of pathological anxiety and deregulation of the hypothalamus-pituitary-adrenal axis when stressed, which clinically manifests itself via anxious behavior and vegetative dystonia with a wide spectrum of somatovegetative symptoms like high irritability, sleep disorders, gastrointestinal spasms, high heart rate, high fatigability, muscular spasms and aches, tingling sensations in the face, body, and limbs [13-14]. Thereby, the magnesium deficiency determines an apparent vegetative imbalance in the form of sympathicotonia, and a high risk of headache chronization (OR = 11.2, 95% CI [5.8; 21.9], $p < 0,001$) [5].

HEADACHE THERAPY GUIDELINES

Like adults, children with headache shall receive mixed treatment. When treating primary headaches, a child shall have all the possibilities for a healthy lifestyle, including balanced nutrition, sufficient fluid intake, limited exposure to noise, as well as reasonable and controllable intake of the over-the-counter painkillers. Older children shall be taught how to relax and deal with stress. Relaxation techniques include deep breathing, yoga, meditation, and progressive muscular relaxation. Biological feedback teaches the child to control body reactions which help to reduce pain intensity. Cognitive behavioral therapy may help the child to handle stress, and to decrease frequency and intensity of the headache.

Headache alleviation drugs are acetaminophen and ibuprofen. Care shall be taken when prescribing acetylsalicylic acid to a child or an adolescent so as to avoid Reye syndrome, which is a rare but potentially fatal condition. Specific anti-migraine medicines, such as triptans, are efficient, but usage thereof in children is limited.

Despite a wide range of therapy techniques available to adults, children often experience headaches that become more frequent with age; symptoms may change to amplify social distress and adaptation of those patients when they become older, which leads to high headache prevalence in the adult population (78-90%) [5].

MAGNESIUM-BASED DRUGS IN HEADACHE TREATMENT

Taking into account the fact that magnesium is an important part of the headache pathogenesis, magnesium-based medicines are considered necessary for mixed treatment. Administration of magnesium-based drugs stabilizes functioning of NMDA-receptors, increases energy metabolism rate, improves lactate disposal, and protects muscles from the spasmodic noci-influence. This defines the clinical effect of magnesium-based drug usage, which manifests itself in the ache frequency reduction [11, 15, 16].

Assuming the fact that Mg^{2+} ions are versatile natural stabilizers for the NMDA receptor subtypes, and do control the functioning of the voltage-gated ionic channel for the Ca^{2+} , Na^+ , K^+ ions, inclusion of the magnesium-based medicines into the basic treatment of somatovegetative, anxiety, and anxiety-depressive headache-associated disorders has been drawn into discussion [13-14].

As of now, it has been proved that the best bioavailability is featured by the bioorganic magnesium compounds like citrate, pidolate, lactate, and orotate, esp. magnesium citrate and pidolate which display the best bioavailability when combined with pyridoxine (B_6^* vitamin) as compared to non-organic magnesium salts. In Russia, magnesium-based drugs with evidence bases, allowed for pediatric usage, are available in the form of the following bioorganic salts.

1) Magne B_6 is a solution for intake, which contains magnesium lactate 186 mg, and magnesium pidolate 936 mg, which is equivalent to the total of Mg^{2+} 100 mg and pyridoxine 10 mg, i.e. B_6 vitamin. This allows for a quick serum magnesium increase. It is allowed for over-1 children. The daily dose is 10-30 Mg^{2+} mg per kilogram of body weight distributed between 2-3 intakes. For instance, if the patient weighs 10 kg or more, the daily dose is 1-4 ampules of Magne B_6 [17,24].

2) Magne B_6 Forte is a tablet drug that contains 618.43 mg of magnesium citrate, which is equivalent to the total of 100 mg Mg^{2+} and 10 mg pyridoxine. It is allowed for over-6 children. The daily dose shall be no less than 10-30 mg of Mg^{2+} per kilogram of body weight distributed between 2-3 intakes. For instance, if the patient weighs ca. 20 kg, the daily dose is 2-4 pills per day distributed between 2-3 intakes. Pills should be taken with food [17,24].

* Bioorganic magnesium salts are the most bioavailable compounds, whereas the bioavailability of non-organic salts does not exceed 5% (magnesium hydroxide). Bioavailability of magnesium citrate is 33%, and that of magnesium pydolate is 43%. Bioavailability of magnesium citrate increases up to 50% when combined with pyridoxine, i.e. B₆ pyridoxine is a natural “magnesium stabilizer” in the human body, as it increases the Mg²⁺ content in blood plasma and erythrocytes and decreases magnesium-urea [17–18].

Unlike non-organic salts, magnesium citrate does not have a negative impact on the digestive tract's mucosa and features a greater tolerance [17]. Use of magnesium citrate improves Mg²⁺ uptake as compared to magnesium lactate and other organic compounds, if the gastric acidity is reduced [19].

Bioavailability is not the only feature of magnesium citrate, which also has several specific molecular effects. The citrate participates as the median Krebs cycle substrate of interaction with dicarboxylate carrier proteins and is also specific from the point of view of physical and chemical molecular properties. It ought to be emphasized that citrate metabolites are essential endogenous molecules. An almost full conversion of the citrate into carbon dioxide and water makes it a perfect magnesium carrier. The bioavailability of magnesium citrate facilitates normalization of water and mineral urine fraction balance, and also helps to reduce crystal formation in urine. Solubility and weakly alkaline reaction result in blood alkalization, which consequently leads to alkalization of other body fluids like urine, synovial fluid, etc. The acid-alkali balance is normalized; this prevents formation of calculi in kidneys, bile ducts, salivary glands etc. [17–18].

Prolonged magnesium-based drug course has been accepted as an alternative technique of preventing migraine in children [20].

Magnesium pydolate is important in treating tension headache in children. A 3-month-long 2.25 g/day magnesium pydolate monotherapy administered to children and adolescents with occasional tension headache has shown a significant impact of magnesium deficiency elimination on clinical manifestations: headache episodes have become 69.9% less frequent, analgesic intake was reduced by 65.4%. The general working capacity increased by 75.7% [21].

For patients with headache, magnesium deficiency prevention is crucial, including nutrition changes. A frequent magnesium deficiency cause is modification of the nutritional status by consuming a huge amount of salt, including “hidden” salt in sausages and other processed foods, refined foods that contain a lot less magnesium and excessive amounts of calcium, phosphorus, proteins and fats that decrease magnesium intake due to formation of non-absorbable magnesium complexes. In adolescents, it may also be caused by alcohol, psychostimulants and other

psychoactive substances. A patient with headache shall be provided with sufficient magnesium intake with food and water. Children need larger doses as they grow. The doses are as follows: under-3 children – 50-150 mg per kilogram of body weight; 4-6-year-old children – 200 mg; 7-10-year-old – 250 mg; 11-17-year-old – 300 mg; for adults, the dose is only 6 mg per kilogram of body weight [3, 10].

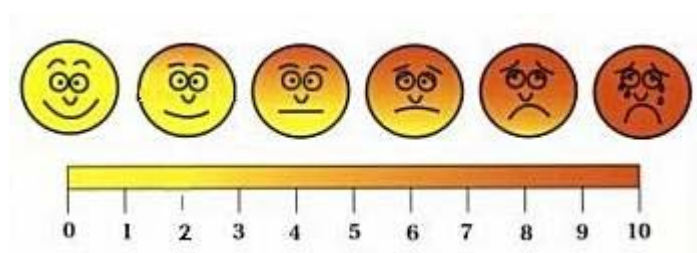
Therefore, results of the studies carried out in the last two decades allow for a statement that low Mg^{2+} concentration is a universal link in headache pathogenesis. Inclusion of magnesium-based medicines combined with pyridoxine (Magne B₆ Forte or Magne B₆ drinkable solution) into the basic headache therapy in order to modify cellular metabolism in children and improve their adaptability allows considering elimination of magnesium deficiency one of the conditions for successful headache treatment and prevention of headache progression or chronization [22-23].

Appendix 1. Headache Log

Date and Time of Pain Occurrence	Ache Intensity	Ache Cause	Ache Alleviation / other comments

Note. Headache Scale: 1 – mild headache, which does not disturb everyday activity; 2 – moderate headaches, which causes anxiety, but does not disturb everyday activity; 3 – severe pain (normal activity is infeasible, bed rest is required). Older persons and adolescents may also refer to the visual analog scale to evaluate severity of the pain syndrome.

Visual Analog Headache Intensity Scale



Patient are also requested to fill in the Headache Log what they have managed to do during the headache.

Pain triggers are to be filled:

- 1) Paracenesesthesia secondary to influenza or general paracenesesthesia;
- 2) Tiredness;
- 3) Physical stress;
- 4) Overheat and sultriness;
- 5) Sunlight flecks;
- 6) Stress;
- 7) Missed meal or long starvation;
- 8) Consumption of nuts;
- 9) Consumption of onions;
- 10) Consumption of salty foods;
- 11) Redundance of caffeine;
- 12) Consumption of chocolate;
- 13) Consumption of citrus;
- 14) Consumption of air-dried meat;
- 15) Missed drug intake;
- 16) Other reason.

It is also necessary to fill in the last column to indicate what allowed alleviating the pain:

- 1) A vessel with ice;
- 2) Bed rest;
- 3) Unlit bedroom;
- 4) Paracetamol or other drugs;
- 5) Relaxation techniques;
- 6) Other.