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Magnesium deficit as a modern nutritional issue in children and adolescents

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The review is dedicated to the issues of body magnesium deficit. The authors used data of the evidence-based trials. The authors consider pathologic conditions predisposed by magnesium deficit, i.e. excess weight and obesity, attention deficit and hyperactivity disorder, impaired glucose intolerance, arterial hypertension, gallstone disease and other conditions in detail. The authors dwell upon ways of magnesium deficit correction. The article shows that the most effective method is application of organic magnesium salts (lactate, pidolate, citrate).
Key words: *magnesium deficit, metabolic syndrome, excess weight, obesity, attention deficit and hyperactivity disorder, impaired glucose intolerance, arterial hypertension, gallstone disease, correction, magnesium pidolate, magnesium citrate, children.*

INTRODUCTION

Irrational nutrition is one of the key reasons of low life quality; it determines programs of children's and adolescents' negative development and early age of onset of various diseases, including the so called lifestyle diseases, to a large extent. Eminent Russian pediatrician, Igor Mikhaylovich Vorontsov, stated a sad fact in his commencement address dedicated to the 80th anniversary of the Saint Petersburg Pediatric Academy: "In 1987, that is, when Russia entered the so called perestroika period, the state shunned the responsibility to protect children's health and nutrition; since then, Russia has lost the state approach to regulating nutrition of children and adolescents. The responsibility for children's nutrition concerns was completely shifted to families, which are in many cases poverty-ridden and incompetent in the issues of children's rational nutrition. Decline in all children's health parameters in the last 20 years is without any doubt associated with nutrition system changes among other things" [1]. The main disadvantages of the modern children's nutrition are high-caloric carbohydrate foods, abundance of chemical colorants, leavening agents, flavor enhancers, preservatives, wetting agents, excessive consumption of saturated animal fats and common salt and insufficient consumption of quality plant foods, fish, milk, safe drinking water and micronutrients.
Magnesium (Mg) is one of the most "lacking" micronutrients in the modern children's nutrition in Russia and many other countries. Indeed, the center constituent of chlorophyll and component of heavy mineral water, magnesium content in children's nutrition, especially in adolescents' nutrition, is insufficient. At the same time, there has recently appeared an extremely negative tendency of widespread departure from the traditional diet to the use of nutrient substances removing magnesium from a child's body (artificial colorants, energy caffeinated drinks, coke-type drinks, oversalted foods, early use of alcohol, smoking etc.). Let us consider the issue of "magnesium hunger" in children in more detail.
Magnesium deficiency causes susceptibility to arterial hypertension, obesity, cholelithiasis and a range of ther pathological conditions.

Magnesium is one of the most important bioelements of key significance for maintaining metabolic functions. Mg^{2+} ions and pyridoxine derivatives are cofactors of numerous enzymes taking part in lipid and carbohydrate metabolism, including insulin signaling pathways [2]. Magnesium deficiency characteristic of the so called civilized nutrition along with insufficient consumption of pyridoxine and other group B vitamins results in decreased biological activity of these enzymes.

Insufficient magnesium supply is observed even in diets of some healthy children. Examination of healthy 7-8-year-old girls of health groups I and II (n = 43) established that the average hair magnesium content in 88% of them was 79.86 ± 7.18 mcg/g (within biologically acceptable level – 19-163 mcg/g). Hair magnesium content was 20% below the lower threshold only in 12% of the examined (15.29 ± 0.36 mcg/g). Children with magnesium deficiency were also characterized by high body mass index (BMI; $p < 0.001$) and low hand muscle contraction strength parameters ($p < 0.001$) [3]. Calcium and magnesium consumption may be insufficient even in preschool-aged children. Thus, examination of 90 preschoolers (3 groups of 3-, 4- and 5-year-old children, each involving 15 boys and girls) in Japan established that the average daily consumption of calcium, magnesium, potassium and sodium was 432 mg, 110 mg, 1.18 g and 1.60 g, respectively. Low calcium consumption in most preschoolers is due to the traditionally insufficient consumption of milk and dairy products in Japan. Magnesium consumption was below the established standard in 13% of children. These children were characterized by higher body weight and heart rate [4]. It ought to be noted that the Japanese nutrition is distinguished by high sodium consumption with common salt and salty soy sauces. Common salt (NaCl) – a powerful food substance – is the second best magnesium remover from the body (with urine) after alcohol [2]. Thus, children as young as 7-8 years of age with magnesium deficiency have developmental deviations: negative tendency to the development of arterial hypertension, high risk of obesity and drop in growth rate [2-4].

Examination of 7-10-year-old children in Turkey detected a connection between *micronutrients supply and linear growth*. Ultimate analysis of whole blood and hair of children with growth inhibition (n = 27) yielded significantly lower levels of Fe and Zn in blood ($p < 0.05$) and of Fe, Zn, Ca and Mg in hair ($p < 0.05$) than in the control group children (n = 21) [5].

Magnesium deficiency aggravates by adolescence. E.g., examination of 5,060 1-11-year-old children and Mexico revealed low blood serum magnesium level only in 12% of the 1-4-year-old children. Hypomagnesaemia was revealed in 28% of the older children (5-11-year-old) [5]. Another large-scale trial performed in Mexico, which involved examination of 2,447 12-19-year-old adolescents regarding levels of blood serum nutrients, revealed that deficiency of magnesium was the worst. Iron, copper, zinc and magnesium deficiencies were revealed in 6.9, 14 and 12 (girls and boys), 28 and 25, 40 and 35% of adolescents, respectively. Magnesium-lacking children and adolescents were characterized by higher BMI and stress level; girls suffered from menstrual disturbances more often [6]. A large-scale examination of children in Pakistan demonstrated that magnesium deficiency is associated with nyctalopia (avitaminosis and hypovitaminosis A) and excessive consumption of preserved, dried and salty foods. Visually impaired school students had considerably lower levels of magnesium, calcium and potassium in blood serum and hair and higher sodium levels than the control group children [7]. Sodium entered children's bodies not only with common salt, but also with a flavor enhancer – sodium glutamate, excessive consumption of which is associated with such visual impairment as myopia. Myopia is observed considerably more often in children and adolescents from those countries where sodium glutamate is actively used in the system of fast and convenience (bouillon cubes, instant noodles etc.) food. Such countries include China and Singapore [8, 9].

Moreover, chronic magnesium and zinc deficiencies were established in children with acute lymphoblastic leukemia (ALL) and malignant lymphomas (groups of 38 children with lymphomas and 12 healthy children). The average hair magnesium levels were considerably lower in patients than in the control group, especially in the patients with T-cellular ALL form (28.9 ± 3.9 mcg/g, control group – 87.6 ± 18.5 mcg/g; $p < 0.05$) [10].

European trials regarding magnesium in children also demonstrate connection of low magnesium *diets*, low hair magnesium level, early onset of atherogenic disorders and obesity. Thus, an examination of 218 5-10-year-old girls in Belgium established inverse correlation of hair calcium and magnesium content with certain parameters (diastolic blood pressure, homeostasis insulin resistance evaluation models, levels of high-density lipoproteins, cholesterol and BMI). Considerable decline in both calcium and magnesium levels was established in girls with each of the parameters above the age 75th percentile [11].

A range of large-scale NHANES trials performed in the USA confirms a growing "magnesium-lacking trend" in the modern children's nutrition. Cohorts of 1-5 year-old children were examined in different years. NHANES trials in 1976-1980, 1988-1994 and 2001-2006 demonstrated that ca. 85% of children consumed milk in 1976-1980 and only 77% - in 2001-2006. In 1976-1980 consumption of colored and flavored milk (containing artificial pink colorants and strawberry and cherry flavors, yellow pineapple colorants etc.) was relatively low (less than 3%), whereas by 2006 it increased to 14% ($p < 0.001$). Consumption of fruit juices and lemonades has increased as well. Thus, more than 50% of the US population had started to consume packaged juices by 2006 (in comparison with 30% in 1976-1980) ($p < 0.001$). Up to 30% of children in the USA had started to consume the so called nonalcoholic beverages, lemonades and coke-type drinks containing large amounts of colorants and trace magnesium by 2006. There is a widely spread wrong belief that fruit juices are a source of magnesium for children as well. Even 1 l of a 100% juice per day may compensate only up to 11% of the recommended daily magnesium consumption, whereas nonalcoholic beverages are sources of none micronutrients, including magnesium [12].

Negative tendencies in children's nutrition and magnesium-lacking diets form insulin resistance from childhood. Low serum magnesium levels are associated with obesity and insulin resistance in children. Examination of 203 children and adolescents (117 – with obesity, 86 – control group) demonstrated that serum magnesium levels were considerably lower in the children with obesity than in the control group ($p = 0.014$). At the same time, healthy children featured a positive correlation of blood serum magnesium level with BMI ($p = 0.03$). In other words, in the event of no obesity, high magnesium levels correspond to higher body weight and are proportional to taller stature, whereas in the event of obesity this correlation is altered. Excess body weight in the event of normal and, especially, short stature is clearly associated with magnesium deficiency [13].

It ought to be noted that physiologically magnesium is necessary for energy metabolism – processes of breaking proteins, fats and carbohydrates down and transforming them into adenosine triphosphate (ATP). More than 310 of the 720 identified magnesium-dependent human proteome proteins take part in ATP metabolism. In particular, magnesium is necessary for transmitting signals from insulin receptors and breaking glucose down efficiently.

Magnesium is an important mediator of both carbohydrate and lipid metabolism, which is why low blood plasma magnesium levels are associated with higher intensity of obesity and metabolic syndrome. E.g., observation of 117 patients with excess weight and obesity demonstrated that the lower the magnesium levels, the larger the number of metabolic syndrome components characterizing the patient's condition [14-18].

Susceptibility to magnesium deficiency and development of obesity and metabolic syndrome may be evaluated by examining the child's genetic passport. Magnesium is a cofactor of 720 proteins, which is why magnesium deficiency negatively affects biological activity of genes and the magnesium-dependent proteins that they encode. The modern method of bioinformational analysis helped to determine the genes, impaired activity of which results in lipid metabolism anomalies and contributes to the development of metabolic syndrome secondary to the insufficient magnesium consumption with food [2]. A list of genes/proteins, decreased activity of which in the setting of magnesium deficiency contributes to the development of lipid metabolism disorders, was established on the basis of the analysis (tb. 1). These proteins are associated with lipid metabolism and its regulation.

Table 1. ***Magnesium-dependent genes / proteins of lipid metabolism. In the event of magnesium deficiency, gene activity of these proteins decreases and dyslipidemia starts to form [2, 17, 19]***

Protein	Genes	Function
Lipid metabolism		
ATP citrate synthase	ACLY	Synthesis of cytosolic acetyl-coenzyme A and lipids
Medium-chain fatty acid acyl-CoA synthetases	ACSM1, 2, 3, 4, 5, 6	Synthesis of medium-chain fatty acids
Lecithin-cholesterol acyltransferase	LCAT	Maintenance of normal levels of triglycerides and HDLs
Long-chain fatty acid ligase 1	ACSL1	Activation of long-chain fatty acids for synthesis of cell lipids and degradation in the process of beta-oxidation. Preferable substrates: palmitate, oleate and linoleate
Long-chain fatty acid ligase 3	ACSL3	Hepatic lipogenesis, preferable substrates: myristate, laurate, arachidonate and eicosapentaenoate
Long-chain fatty acid ligase 4	ACSL4	Arachidonate and eicosapentaenoate
Long-chain fatty acid ligase 5	ACSL5	Activation of fatty acids from exogenous sources for synthesis of triglycerides of C16-C18 unsaturated fatty acids
Lipid metabolism regulation		
Phosphatase 2 and 3 phosphadate	LPIN2, 3	Control of fatty acid metabolism. Catalyzes transformation of phosphatidic acid into diacylglycerols during synthesis of triglycerides, phosphatidylcholine and phosphatidylethanolamine Co-activator of PPARGC1A transcription factor, which regulates lipid metabolism
Peroxisome proliferator-activated receptors	PPARA, B, C, D	Cholesterol biosynthesis regulators
AMP-activated protein kinase alpha	PRKAA1, 2	Cuts off cell's biosynthetic pathways in the event of decrease in magnesium-ATP levels and accumulation of 5' AMP at hypoxia. Regulates synthesis of fatty acids by phosphorylation of acetyl-CoA carboxylase. Cholesterol synthesis regulation by means of inactivating hormone-sensitive lipase and hydroxymethylglutaryl-CoA reductase

Note. HDLs – high-density lipoproteins.

Magnesium is an integral constituent of active enzyme centers, which is why magnesium deficiency contributes to inevitable decline in the activity of these proteins, which results in lipid biotransformation rate decrease. Lipid metabolism activity decline, impaired lipid metabolism regulation and signal transmission from adrenergic receptors leads to energy metabolism intensity decline and blood plasma lipid imbalance. In particular, *hypomagnesaemia* inevitably leads to the increase in the levels of plasma triglycerides (due to decreased activity of genes *ACSM1, 2, 3, 4, 5 and 6; ACSL1, 2, 3, 4 and 5; LPIN2 and 3*) and decrease in the levels of high-density lipoproteins (HDLs; decrease in the activity of LCAT, PPARA, B, C and D; PRKAA1 and 2); this is actually observed in the event of abdominal obesity and metabolic syndrome in children of all ages [20-22]. In girls this type of obesity is observed in case of ovarian scleropolycystosis and disturbs menstrual and reproductive functions.

Cholelithiasis has also started to appear at a younger age, especially taking into consideration the rate of diet mistakes and magnesium deficiency in children's nutrition. Long-term consumption of physiologically sufficient magnesium doses decreases the risk of gallbladder dyskinesia and cholelithiasis. On the contrary, magnesium deficiency contributes to development of dyslipidemia – one of the physiological causes of bile congestion. Correlation of magnesium consumption with the risk of cholelithiasis has been studied for 16 years of diet observation.

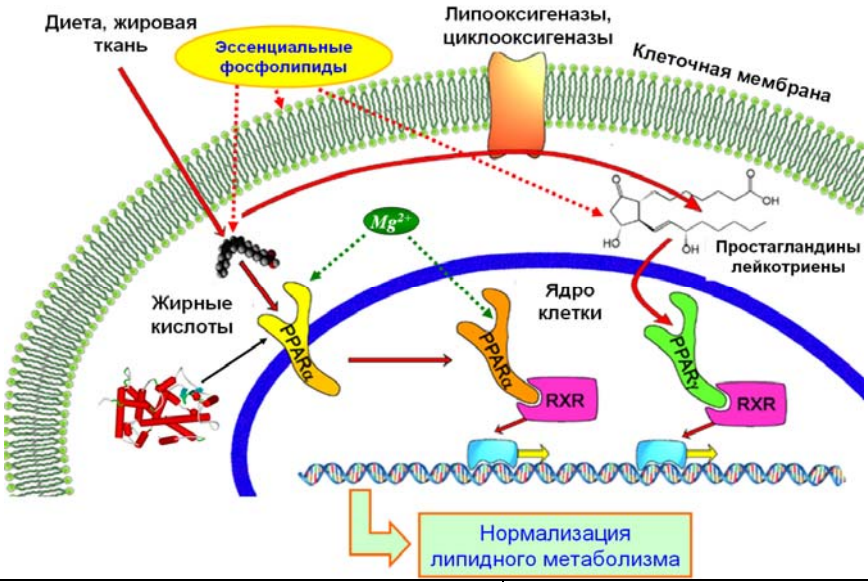
Magnesium consumption was assessed with a verified diet questionnaire. 2,195 cholelithiasis cases were registered. Comparison of subgroups with the lowest and the highest magnesium consumption demonstrated the disease risk reduction by 33% in the event of higher magnesium consumption (odds ratio – 0.67; confidence interval – 0.59-0.77; $p < 0.0001$) [21].

Magnesium ions are necessary for maintaining activity of enzyme *lecithin-cholesterol acyltransferase* (LCAT). Sufficient level of LCAT activity is necessary for maintaining normal levels of triglycerides and HDLs [14]. Enzyme LCAT is a central plasma lipoprotein metabolism enzyme. Synthesized in liver, LCAT is secreted to plasma, where it links with lipoprotein particles. The enzyme transforms free cholesterol into cholesterol ethers, which are further absorbed by a lipoprotein particle's nucleus. Activity of enzyme LCAT depends on free essential phospholipids, also known as "lecithins", to a large extent.

LCAT activity levels are in inverse proportion to leptin levels and obesity [22]. The severest clinical manifestations of LCAT activity deficit are observed when patients have gene *LCAT* defects. The gene defects lead to congenital LCAT insufficiency (OMIM code - 245900) characterized by blood plasma cholesterol etherification depression and cholesterol sediments in vessels, liver and other organs.

Biochemical experiments demonstrated that magnesium is necessary for activity of enzyme LCAT. Thus, acute magnesium deficiency was caused by and 8-day-long magnesium-lacking diet. Acute magnesium deficiency was accompanied by increase in the levels of plasma triglycerides and free cholesterol and decrease in the level of etherified cholesterol. Blood plasma lecithin-cholesterol acyltransferase activity decreased considerably in the setting of acute magnesium deficiency (on the average – by 54%) [23]. Significant correlations of ionized plasma magnesium, HDL-cholesterol ($r = 0.31$; $p = 0.0345$) and apolipoprotein A-1 ($r = 0.39$; $p = 0.0124$) with LCAT activity ($r = -0.52$; $p = 0.0184$) were observed in the group of 47 children [24].

Pic. 1. ***Biological roles of PPAR proteins contributing to excretion of excess cholesterol. Activity of PPAR proteins depends on intracellular magnesium levels***



Диета, жировая ткань	Diet, adipose tissue
Липооксигеназы, циклооксигеназы	Lipoxygenases, cyclooxygenases
Клеточная мембрана	Cell membrane
Эссенциальные фосфолипиды	Essential phospholipids
Жирные кислоты	Fatty acids
Простагландины, лейкотриены	Prostaglandins, leukotrienes
Ядро клетки	Cell nucleus
Нормализация липидного метаболизма	Lipid metabolism normalization

Moreover, magnesium is also necessary for activity of an important group of cholesterol biosynthesis regulators – *peroxisome proliferator-activated receptors* (PPARs), insufficient activity of which is characterized by pleiotropic effect on atherosclerosis pathophysiology [24]. E.g., protein PPAR-delta (peroxisome proliferator-activated receptor, type δ) activates beta-oxidation processes of fatty acids and contributes to excess cholesterol excretion. Examination of 2,000 patients with ischemic heart disease and healthy patients (control group) demonstrated that gene *PPARD* polymorphisms determine plasma lipid levels and coronary atherosclerosis severity. Magnesium plays a certain role in regulating signaling pathways of PPAR proteins (pic. 1) [24]; hydrolysis of essential phospholipids results in the formation of PPAR-ligands. Thus, magnesium contributes to activation of several key factors of lipid metabolism and facilitates processing of saturated animal fats. Along with insufficient physical activity, excess caloric content and micronutrient deficiency of the foods consumed by children, magnesium deficiency in a diet provokes accumulation of excess visceral fat.

Magnesium constitutes or is a cofactor of most neurospecific proteins, such as glial fibrillary acidic protein (GFAP), S-100, neuron specific enolase (NSE) etc. [25-26]. NSE is a dimeric metal-activating protein containing two magnesium ions per subunit: one fixed conformation ion and one catalytic ion linked to enzyme-substrate complex and inducing catalysis [27]. Thus, magnesium is necessary for dimer catalysis and stabilization. It has been demonstrated that magnesium links with all protein S100 forms, although S100 affinity for calcium becomes lower in the presence of magnesium and potassium [28]. Therefore, magnesium may serve as a neuroprotectant and play an important role in regulating permeability of the hematoencephalic barrier, which is concomitant to various neurological pathologies.

Thus, magnesium-lacking diet in children of different age living in different countries has become a common phenomenon in view of the nutrition profile that has been changing for the last 20-30 years. At the same time, the risk of such unusual for pediatrics issues as childhood and adolescent obesity, insulin resistance, metabolic syndrome, arterial hypertonia from adolescence and young age, lymphomas, vision disorders has been increasing, along with the increase in the number of children and adolescents with hyperactivity and attention disorder. Despite the fact that magnesium deficiency is present in the child's diet and body at all of the aforementioned pathological conditions, it is more often present and may be the worst in the event of the child's hyperactivity.

Magnesium deficiency as pathophysiological core of hyperactivity

Attention deficit and hyperactivity is a difficult medical social and medical pedagogical issue. Stable increase in the number of children and adolescents with deviant forms of behavior featuring a distinct component of hyperactivity, disinhibition and low cortical control has been observed in Russia in the last 20-30 years. There are many reasons to that, including social issues. Family system breakdown and orphanhood despite the living parents, fast corruption of the society and loss of ethics, pivotal nutrition system change (the so called grown-up nutrition from small and preschool age) inevitably increase the population of problem children and adolescents. Hyperactivity and attention deficit and hyperactivity disorder result from the interaction of social, medical, genetic, nutritional and other factors, including regular alcohol consumption by parents.

It is known that the widespread *hyperactivity* and the less frequent attention deficit and hyperactivity disorder (ADHD) result from a range of causes, many of which are completely ignored not only by parents, but also by many medical specialists. These reasons include negative influence of the aggressive information environment, deficits of numerous micronutrients (magnesium, iodine, omega-3 polyunsaturated fatty acids etc.), excess of a range of neurotoxins in the mother's body during pregnancy (lead, nicotine, alcohol), certain genetic polymorphisms etc.

Magnesium is a central element maintaining balance of excitation-inhibition processes in the central nervous system. Firstly, magnesium is necessary for stabilizing activity of excitatory (glutamate) receptors. Secondly, magnesium is an essential cofactor of adenylate cyclases, which take part in signal transmission from dopamine, serotonin and adrenalin receptors to the main intracellular cascades. Thirdly, as has been mentioned before, magnesium is also a cofactor of enzyme Catechol-O-methyl transferase, which inactivates excess of monoamine neurotransmitters [2, 15].
Analysis of biochemical factors of attention deficit and hyperactivity disorder demonstrates that ADHD is characterized by *numerous* nutrition disorders (tb. 2).

Table 2. ***Nutritional factors increasing the risk of hyperactivity and attention deficit and hyperactivity disorder [17]***

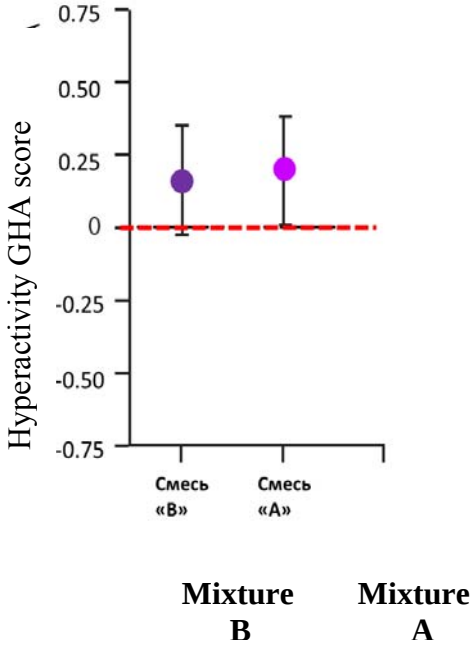
Excesses	Deficiencies
Artificial food colorants (E110, E104, E122, E129, E102, E124) – brightly colored sweets, cookies, candies, sodas and canned foods	**Magnesium deficiency** (insufficient consumption of fresh green leafy plants, vegetables, fruits, nuts and fish)
Excess of neurotoxicants (lead, nicotine, alcohol, smoking, pesticides, polychlorinated biphenols, polyfluoroalkyls) – water, environmental and food pollution	**Deficiency of omega-3 PUFAs** (insufficient consumption of fresh fish)
Hyperphosphoric diet (various types of sausage)	**Iodine deficiency** (insufficient consumption of seafood, seaweeds and sea fish)
Oversalted food	**Deficiency of zinc, iron and copper** (quality meat, nuts, seeds and red grapes)
Excessive consumption of saturated solid fats (butter and other dairy products, low quality fatty beef and pork, margarine)	**Safe drinking water consumption deficiency**

Note. PUFAs – polyunsaturated fatty acids.

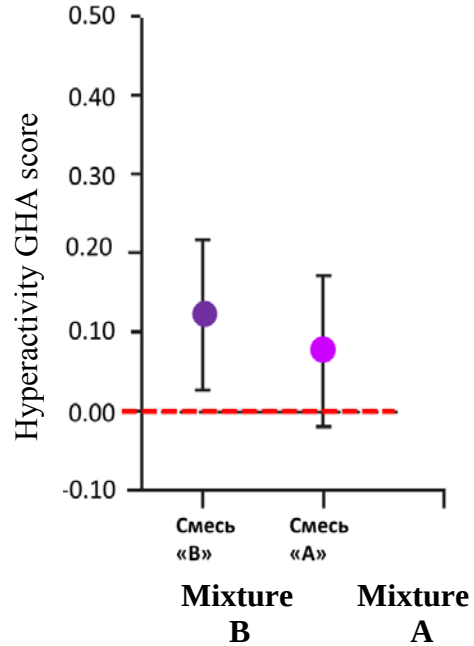
Scientists list a range of factors increasing the risk of hyperactivity development. E.g., trials indicate connection between cigarette smoking and alcohol consumption during pregnancy and hyperactivity development in children [17]. Preschool-aged children subject to high lead levels (paint, tainted drinking water, smoking of parents/peers, exhaust etc.) are also susceptible to high risk of ADHD. Apart from lead and tobacco thermal decomposition products, many other xenobiotics result in the increase in hyperactivity risk. A Southampton examination of children established correlation of food additives E102, E104, E110, E122, E124 and E129, which lead to magnesium excretion from the body, with children's hyperactivity [29].
The examination involved a group of 153 3-year-old and 144 8-9-year-old children. The children had not been consuming foods containing the colorants used in the trial for 6 weeks. All children received only a placebo juice (without colorants and sodium benzoate) during weeks 1, 3 and 5; during weeks 2, 4 and 6 the group of children was randomized to receive 300 ml/day of juice containing a combination of colorants (mixture A or mixture B).
For 3-year-old children, mixture A contained 20 mg of artificial food colorants: 5 mg of Sunset Yellow [E110], 2.5 mg of carmoisine [E122], 7.5 mg of tartrazine [E102], 5 mg of Ponceau 4R [E124] and 45 mg of sodium benzoate [E211]. Mixture B contained 30 mg of artificial food colorants: 7.5 mg of Sunset Yellow, 7.5 mg of carmoisine, 7.5 mg of Quinoline Yellow [E110], 7.5 mg of Allura Red AC [E129] and 45 mg of sodium benzoate.

Doses of all colorants were 1.25 times higher for 8-9-year-old children. Children's hyperactivity was assessed on a weekly basis using a complex GHA (Global Hyperactivity Assessment) scale. The trial results demonstrated that a week-long intake of a mixture of colorants is enough to result in a significant increase in hyperactivity parameters (GHA scale) both in 3-year-old (pic. 2) and 8-9-year-old children (pic. 3). It should be noted that the effect of artificial food colorants on 3-year-old children's hyperactivity was far worse in comparison with the group of 8-9-year-old children. E.g., GHA score increase for mixture A in comparison with the placebo group was + 0.22 ± 0.16 in 3-year-old children and only + 0.08 ± 0.12 in the group of 8-9-year-old children.

Pic. 2. ***Effect of food colorant mixtures (mixture A, mixture B, see the main body) intake on hyperactivity GHA (Global Hyperactivity Assessment) scale parameters in 3-year-old children. 95% confidence intervals are shown. The dashed line indicates the placebo effect (according to McCann, 2007)***

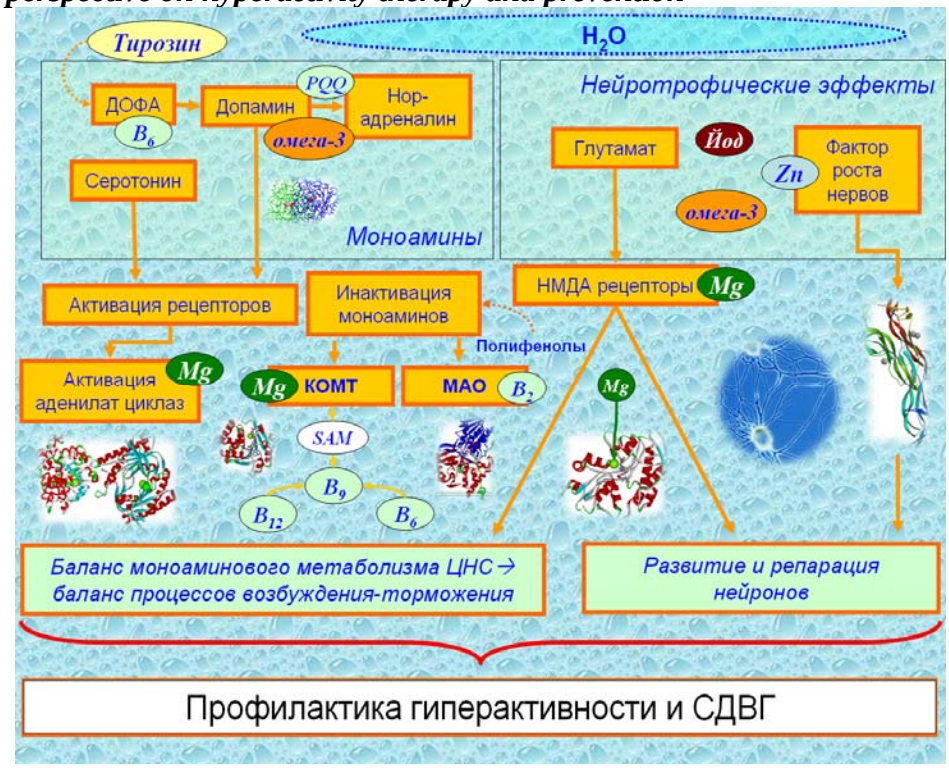


Pic. 3. ***Effect of food colorant mixtures (mixture A, mixture B, see the main body) intake on hyperactivity GHA (Global Hyperactivity Assessment) scale parameters in 8-9-year-old children. 95% confidence intervals are shown. The dashed line indicates the placebo effect (according to McCann, 2007)***



ADHD is associated with seriously imbalanced levels of monoamine neurotransmitters – not only of dopamine, but also of *serotonin, adrenalin and noradrenalin, the metabolism of which depends on magnesium and pyridoxine supply*. ADHD development is affected by low level/activity of monoamine metabolism proteins, low pyridoxine level, excess of lead and copper and deficiency of zinc, iodine and magnesium (pic. 4).

Pic. 4. ***Micronutrients, magnesium; neurochemistry of the central nervous system (CNS): nutritional perspective on hyperactivity therapy and prevention***



Note. ADHD – attention deficit and hyperactivity disorder, COMT – Catechol-O-methyl transferase, MAO – monoamine oxidase.

Моноамины	Monoamines
Тирозин	Tyrosine
ДОФА	DOPA
Допамин	Dopamine
Омега-3	Omega-3
Норадреналин	Noradrenalin
Серотонин	Serotonin
Активация рецепторов	Activation of receptors
Активация аденилат циклаз	Activation of adenylate cyclases
Нейротрофические эффекты	Neurotrophic effects
Йод	Iodine
Глутамат	Glutamate
Фактор роста нервов	Nerve growth factor
НМДА рецепторы	NMDA receptors
Развитие и репарация нейронов	Development and reparation of neurons
Баланс моноаминового метаболизма ЦНС → баланс процессов возбуждения-торможения	CNS monoamine metabolism balance → balance of excitation-inhibition processes
Полифенолы	Polyphenols
Инактивация моноаминов	Inactivation of monoamines
КОМТ	COMT
МАО	MAO
Профилактика гиперактивности и СДВГ	Prevention of hyperactivity and ADHD

Magnesium deficiency was the worst of all the deficiencies; it was observed in more than 70% of the patients. More than 65% of the patients with ADHD had 2 or even more times lower magnesium levels ($p < 0.05$). Hair analysis revealed deficiencies of the following elements (in descending order) in the children with ADHD: Mg (72%) > Zn (67%) > Ca (53%) > Mn (43%) > Co (35%) > Fe (13%) > Se (10%) = Si (10%) > Cr (9%). It is obvious that the core of deficiencies is constituted of 5 metals – Mg, Zn, Cal, Mn and Co ($p < 0.0001$) [17, 18].
Magnesium deficiency in food leads to accumulation of free iron and lead in liver and disturbs hepatic balance of many other essential elements. The experiment involved taking liver samples from all animals and determining content of 36 elements using inductively coupled plasma mass spectrometry (ICP-MS) after a 4-week-long magnesium-lacking diet. Mg deficiency contributed to high levels of free iron (Fe), copper (Cu), zinc (Zn), gallium (Ga), yttrium (Y), zirconium (Zr), molybdenum (Mo), rhodium (Rh), silver (Ag) and barium (Ba) [18].
It ought to be noted that both magnesium deficiency and hyperactivity feature clinically similar symptoms. It is known that Mg deficiency leads to such neurological disorders as increase in the activity of tendon reflexes, ataxia, tremor, disorientation and provokes convulsive state, nystagmus and paresthesias. These physiological manifestations of magnesium deficiency correspond to basic ADHD components, namely, behavioral disorders in the form of impulsion, uncontrollable behavior when stressed, attention deficit and motor deficit, the latter manifested with hyperactivity. Thus, Mg deficiency is specific to attention deficit and hyperactivity disorder and may be seen as a characteristic feature of the nosological elemental pattern in children with ADHD.
Interestingly, low activity of ADCY2, ADCY3 and ADCY4 leads to olfactory deterioration or obtundation. Indeed, not only low intellectual capabilities, but also olfactory and hearing deterioration are observed in children with ADHD [30]. Occurrence of magnesium in the active centers of all human adenylate cyclases indicates that magnesium deficiency may considerably contribute to the olfactory disorders observed in children with ADHD.
As has been aforementioned, magnesium is a crucial micronutrient for ADHD correction. This fact following from fundamental biochemistry is confirmed by a range of clinical trials. E.g., intake of organic magnesium in the groups of children with ADHD (50 children) and children taking placebo (25 children) demonstrated considerable increase in the levels of magnesium, zinc, calcium and considerable decline in the clinical pattern of hyperactivity [31].
It ought to be mentioned that only organic magnesium salts are used in ADHD therapy – lactate, pidolate and citrate (e.g., Magne B_6, Magne B_6 Forte, Magne B_6 drinkable solution) – due to high bioassimilation of organic salts and almost no undesirable adverse effects, which is extremely important for pediatric practice. E.g., magnesium pidolate solution with pyridoxine (ampoules with Magne B_6 solution) is allowed to use in patients over 1 year of age; magnesium lactate and citrate – over 6 years of age. Magnesium replenishment with magnesium citrate (Magne B_6 Forte) is recommended to children with acidosis (or shift towards acidosis) and oxaluria to prevent urolithiasis and compensate fast neuropsychic exhaustion [32].

Diet magnesium deficiency correction and intake of magnesium preparations

It ought to be mentioned that serum magnesium constitutes less than 1% of the total body magnesium content, which is why mere determination of serum magnesium levels is not always sufficient to state hypomagnesaemia. This fact necessitates use of other body magnesium content parameters (magnesium level in erythrocytes and lymphocytes, hair and daily urine magnesium content etc.) and assessment of magnesium content in the diet. Attention ought to be drawn to the magnesium-rich foods (tb. 3).
Concentration of magnesium and the other macro- and micronutrients typical of one and the same product may vary considerably. Thus, the average magnesium concentration in the wheat bran cultivated in Russia is lower (448 mg / 100 g) than the magnesium concentration in the

wheat bran cultivated in Europe. The average magnesium content in various foods is given in tb. 3.

Table 3. ***The average magnesium concentration in various foods [13]***

Food	mg /100 g
Brown algae, especially laminaria	760
Wheat brans	590
Sesame	540
Pumpkin seeds	535
Sunflower seeds	420
Sesame halva	303
Red port wine mixed with molasses	258
Sprouted wheat grains	250
Soy	247
Brewer's yeast	231
Watermelon	224
Almonds*	230-267
Nuts*	158-267
Hazelnuts*	184
Peanuts	175
Walnuts*	131
Dry lactoserum	180
Greens	170
Oat flakes (oatmeal)	142
Kidney beans	130
Brown rice	130
Peas	107
Coconut flakes	90
Dried pitted apricots	105
Dried prunes	102
Whole-grain bread	90
Dried apricots, regular apricots, raisins	60
Dates	58
Shrimps	51
Avocados	45
Parsley	41
Garlic	36
Dandelion greens	36
Bananas	35
Cheeses	30
Sea fish	24-73
Polished white rice	27
Eggplants	16
Beef	20
Chicken	19
Milk	13

Note. * - magnesium assimilation with nuts is extremely low in children.

Treatment with mineral water containing magnesium ions and salts is of high importance to diet correction. And Aristotle said that waters are soils that they travel through.

Magnesium-rich mineral waters are rather rare: e.g., Batalinskiy mineral water (Mg – 1.5199 g/l), Donat (Slovenia) (Mg – 1.26 g/l), Pyatigorsk and Lysogorskaya wells (Mg – 0.647 g/l), Kuka resort waters (well No. 27) (Mg – 0.2315 g/l), Crimean Narzan (Mg – less than 0.2 g/l), Kislovodsk Narzans (Mg – less than 0.2 g/l). Many mineral waters feature trace magnesium (Karmadon – 0.0054 g/l, Sosnevskiy – 0.0868 g/l, Slavyanovskaya – 0.0432 g/l, Yessentuki 17 – 0.0708 g/l, Polyustrovo – 0.006 g/l). It should also be mentioned that children use mineral waters for drinking extremely rarely, which is why this therapy reserve is virtually useless [17]. In the event of magnesium deficiency symptoms, preference ought to be given to drugs containing organs magnesium salts (citrate, lactate, pidolate), as mineral waters contain magnesium in the form of less assimilable nonorganic salts.

Magnesium deficiency correction is based on daily intake of 5-15 mg/kg of Mg++ salts for 1-3 months (depending on the indications); *children need 5-10 mg/kg of magnesium per day* (tb. 4).

Table 4. ***Recommended daily magnesium consumption doses in terms of magnesium salts according to «PDR for Nutritional Supplements. Medical Economics. Thomson Healthcare. 2001»***

Age	Daily magnesium dose
Infants	
0-6 months	30 mg
7-12 months	75 mg
Children	
1-3 years	80 mg
4-8 years	130 mg
Male adolescents	
9-13 years	240 mg
14-18 years	410 mg
Female adolescents	
9-13 years	240 mg
14-18 years	360 mg

Commercialization of deficiency of magnesium and other macro- and microelements has resulted in a large number of magnesium preparations, food and biologically active additives entering the market, negative consequences of which is difficult to predict and trace; however, such consequences occur without any doubt. If a part of the second generation organic magnesium salts, chlorophyll and diet correction are acknowledged optimal for magnesium balance correction, use of such substances as magnesium oxide (MgO) and magnesium chlorate (it ought to be noted that the Ecological Committee of the Russian Federation has determined maximum permissible concentrations of these substances in air and drinking water) is inadmissible (tb. 5). However, these substances are included in many biologically active additives and even pharmaceuticals.

Table 5. ***Maximum permissible concentrations (MPCs) of nonorganic magnesium compounds as potential environmental pollutants***

Magnesium compound	MPC (short-term)*	MPC (average daily)	MPC (temporary)
MgO – magnesium oxide	0.4	0.05	-
$MgCl_2O$ – magnesium chlorate	-	0.3	20

Note. MPC (temporary) – temporary permissible concentration of a chemical substance in waters, mg/l; MPC (short-term) – maximum permissible short-term concentration of a chemical substance in community air, mg/m^3; MPC (average daily) – maximum permissible daily average concentration of a chemical substance in community air, mg/m^3.

Magnesium pidolate solution with pyridoxine (ampoules with Magne B_6 solution) is allowed to use in patients over 1 year of age; magnesium lactate and citrate – over 6 years of age. Magnesium replenishment with magnesium citrate (Magne B_6 Forte) is recommended to children with acidosis (or shift towards acidosis) and oxaluria to prevent urolithiasis.

Out of all the organic magnesium salts, magnesium citrate (salt of magnesium and citric acid) is best to replenish microelements in the framework of complex therapy of obesity in adolescents. It is known that citric acid helps to split fats, accelerates metabolism and eliminates hunger. The citrate is an exceptional form of magnesium in terms of efficacy and safety, as citrate anion takes part in the central energy cycle of each cell – Krebs cycle. Moreover, citric acid salts are rather water-soluble, and citrate anion contributes to renal lithogenesis risk reduction. It is recommended to wash magnesium citrate preparation with the sufficient amount of safe drinking water (150-300 ml). It ought to be noted that insufficient water consumption by children and adolescents leads to retention of endotoxins in the body and contributes to lipid metabolism disorders.

Use of magnesium pidolate results in the best improvement of blood plasma magnesium levels within 2-3 hours, which is important when fast elimination of magnesium deficiency is required [32]. It is possible to recommend a combination of magnesium pidolate with pyridoxine as a drug of choice for replenishing magnesium in small children with excess weight and obesity, as magnesium pidolate has a good compliance profile and is allowed to use in children over 1 year of age.

CONCLUSION

Magnesium-lacking diets have become common among children of different age. Magnesium deficiency in children manifests itself with increase in the risk of such unusual for pediatrics issues as childhood and adolescent obesity, insulin resistance, metabolic syndrome, arterial hypertonia from adolescence and young age etc. All these pathological conditions are associated with chronic magnesium deficiency. The evidence-based trials demonstrate potential of using oral organic magnesium preparations and organic magnesium synergist – pyridoxine (organic magnesium salts – lactate, pidolate, citrate) – as part of the complex therapy of children and adolescents to replenish magnesium and prevent excess body weight and metabolic syndrome. A long-term course prescription of organic magnesium preparations is best for deficiency compensation and filling of magnesium pool.

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