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ASSOCIATION OF MICROELEMENTOS WITH THE RISK OF HYPOCHROMIC ANEMIA IN VEGETARIANS AND VEGANS

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Hypochromic anemias have a significant place in the group of alimentary-dependent anemias. The main cause of it is iron deficiency, as this element is part of hemoglobin. However, a serious clinical mistake is to narrow down any case of microcytic hypochromic anemia to iron deficiency. Copper has a huge influence on heme synthesis through the regulation of iron metabolism. Thus, the body may have enough iron, but under conditions of copper deficiency, it is unable for iron to insert into protoporphyrin to form heme. The incorporation of iron into protoporphyrin is also violated with excessive intake of lead. Its more severe intoxication also increases the hemolysis of red blood cells, thereby exacerbating the course of anemia. Other elements affect the heme synthesis process directly or indirectly, e.g. zinc, manganese, chromium, aluminum, and gallium. All of this determines a significant role of assessing the body's elemental status in the differential diagnosis of hypochromic anemia.

Keywords: vegetarian, vegan, nutrition, iron, copper, lead, hypochromic anemia, differential diagnosis of anemia.

Introduction

Hypochromic anemia is characterized by a reduced hemoglobin content in the red blood cells, which is also often associated with a decreased size of the red blood cells (microcytic

anemia). The violation of the hemoglobin synthesis usually underlies the pathogenesis of this type of anemia and consists of two possible parts: violation of heme and globin synthesis [31, 33]. There is a wide variety of causes of hypochromic microcytic anemia: an unbalanced diet, genetic factors, chronic diseases, tumors, endocrine disorders, medication, and other external factors [6, 31]. Moreover, heme synthesis is predominantly disturbed by nutritional factors (deficiencies or excesses of certain elements) [6]. Genetic factors generally violate globin synthesis, e.g. in the case of thalassemia [31].

Iron. Iron is one of the key elements in hematopoiesis, and its deficiency leads to the development of anemia. Iron deficiency may be caused by a lack of iron in food, a violation of its absorption, as well as an increased need for iron (pregnancy, childhood) and chronic blood loss. Whatever the causes of deficiency are, the result will be microcytic hypochromic anemia. At the initial stages, a pool of spare iron (ferritin, hemosiderin) helps maintain a constant level of hemoglobin and other blood counts. After iron depletion, anemia develops, accompanied by a decrease in serum iron, ferritin, and transferrin saturation with iron. Red blood cells look small (microcytic) and pale (hypochromic) [31, 33].

Iron deficiency is a very common nutritional deficiency worldwide and the main cause of microcytic hypochromic anemia [31, 33]. Data on the status of iron in different population groups vary. So, Deriemaeker et al. showed in their study, that vegetarians rarely consumed an insufficient amount of iron [12], and there was more iron in the vegetarian and vegan diets than in the omnivorous one in the EPIC-Oxford study [49]. However, it is important to remember that children, pregnant women, and premenopausal women need to consume more iron than the average population [18]. As analyzed, vegetarians from these groups consumed insufficient amounts of iron compared with the WHO-recommended standards [12, 21].

Although many plant foods are rich in iron [11], it's presented in a ferric (Fe^{3+}) non-heme form, the bioavailability of such iron is less than 5 %, while the ferrous (Fe^{2+}) heme iron contained in animal products is absorbed in the gastrointestinal tract by 25–35 % [18, 31]. Moreover, the bioavailability of iron is also reduced by oxalates, phytates, polyphenols, which are found in large quantities in many plant products [9, 31], while vitamin C, organic acids, amino acids, and sugars increase it [31, 43]. Vegetarian and vegan diets are rich in both phytates and oxalates, as well as vitamin C and organic acids [23].

Studies show that vegetarians, vegans, and omnivores have approximately the same risk of developing iron deficiency anemia [8]. The incidence of iron deficiency in a Swiss study was also comparable between groups [44]. Skalnaya et al. found no significant differences in the iron concentration in the hair of female vegetarians and omnivores. The patterns were similar in both Russia and Bangladesh [47].

At the same time, there is evidence that vegetarians had a greater risk of iron deficiency anemia [39]. It is noteworthy that ferritin was higher in the plasma of omnivores with a higher iron intake by vegans in Swiss and Finnish studies [15, 44]. It was also confirmed in the 2018 meta-analysis that vegans and vegetarians usually have lower ferritin levels compared with omnivores [22].

Copper. Copper is an essential element for humans, being part of many enzymes and participating in many metabolic processes, including hematopoiesis [18, 36]. So, copper is an important component of hephaestin and ceruloplasmin. The first promotes the oxidation of iron in enterocytes and its transport into the circulatory system, necessary for its further metabolism, and ceruloplasmin is associated with the transfer of iron from monocyte-macrophage to plasma [36]. Thus, copper deficiency may lead to disruption of iron metabolism and, as a consequence, hemoglobin synthesis. It is also often accompanied by neutropenia and, to a lesser extent, thrombocytopenia [10]. The mechanism of these disorders, how-

ever, is not completely understood. It may be probably due to a decrease in the maturation and differentiation rate of CD34–positive bone marrow stem cells [38].

Copper is found mainly in plant foods (vegetables, mushrooms, legumes, nuts, grains, seeds), as well as in seafood [37]. Copper deficiency can develop under the influence of nutritional factors, moreover, it must be considered that the need for copper increases during childhood, pregnancy, and lactation [36]. Also, the copper status may depend on zinc intake. The transport of these elements in the digestive tract is carried out using similar mechanisms. If zinc is ingested in excessive amounts, it induces the synthesis of metallothionein in enterocytes, which binds zinc; then these cells are sloughed off into the gut lumen. This mechanism helps prevent excess zinc from entering the bloodstream. However, metallothionein has a greater affinity for copper than for zinc, so the entry of the former into the blood reduces [14, 36]. Besides, iron supplementation can also negatively affect the copper status, as these elements are transported the same way [10].

Vegan and vegetarian diets are rich in copper [1, 23]. The EPIC-Oxford study showed that vegans consumed the highest amount of copper, while omnivores – the smallest [49]. In a Hunt and Vanderpool study, the bioavailability of copper from a vegetarian diet was lower (33 %) than from an omnivorous one (42 %) [24]. This may be due to the high level of phytates and dietary fiber in the vegetarian diet, which can bind copper in the digestive tract and interfere with its absorption. Despite its lower bioavailability, Hunt and Vanderpool showed that the amount of copper absorbed in the digestive tract by vegetarians was still higher since this diet is richer in copper [24].

Nevertheless, data on the status of copper varies among different groups. In a study by Skalnaya et al. conducted among women in Russia, both vegetarians and omnivores had a slightly reduced concentration of copper in their hair, while in Bangladesh, a significant deficiency was observed in both groups [47]. Krajcovicova-Kudlackova et al. also found no significant differences between the groups [30]. At the same time, in another study, the subjects showed a decrease in the concentration of copper in the blood, hair, and urine in three months after switching to a vegetarian diet [50].

Lead. Lead is a toxic element for humans, harming many systems and processes of the body, including hematopoiesis [35]. The hematotoxic effect is primarily based on the ability of lead to disrupting heme synthesis by inhibiting the enzymes delta-aminolevulinic acid dehydratase (ALAD) and ferrochelatase [20, 35]. It leads to an increase in the activity of the intermediate enzyme δ-aminolevulinic synthetase (δ-ALAS) via the feedback mechanism [2]. The inhibition of ferrochelatase leads to the accumulation of protoporphyrin (heme precursor) in red blood cells, in which iron is replaced by zinc [25]. The content of intermediate products of heme synthesis increases in the blood and urine, while the concentration of hemoglobin itself decreases [2].

At the same time, the ability of lead to bind to a large number of ligands (including SH groups) leads to the inactivation of endogenous antioxidants (glutathione, superoxide dismutase), which increases the oxidative stress already caused by lead in the cell. Oxidative damage to erythrocyte membranes leads to a hemolytic mechanism of anemia development [35]. Schwartz et al. observed in their study a dose-dependent decrease in hematocrit related to blood lead levels and suggested that iron deficiency and excess lead in the blood may have a synergistic effect [45].

The lead content in food is primarily dependent on environmental pollution. Among plant products, it is found mainly in spinach, cruciferous [13], and rice [26]. Nevertheless, its main source is fish and seafood [26]. Data on lead consumption vary in different studies. There is evidence that omnivores consume more lead than vegetarians and vegans [41, 54]. In the French study, lead consumption between groups was almost the same though [16].

It was found that lead levels in blood [26, 53] and nails [34] were lower in vegetarians than in omnivores. At the same time, Jose and Ray showed that the concentration of lead in the blood increases in proportion to the amount of fish in the diet [26]. Also, the hair lead levels tended to decrease after following a vegetarian diet for 3 months, however, the concentration was restored when returning to a mixed diet in the Srikumar et al. study [51]. At the same time, Fløtre et al. did not find differences between the groups when examining women [17].

Other elements. Zinc deficiency has been associated with microcytic anemia [3, 28, 29]. Zinc may affect iron homeostasis due to the induction of the expression of divalent metal iron transporter-1 (DMT1) and ferroportin (FPN1), which are involved in the absorption of iron and its intercellular transport, respectively [5, 29]. Zinc is found in plant foods, but the phytates present in it interfere with zinc absorption, so vegans and vegetarians may be more prone to its deficiency, which is confirmed by numerous studies [18].

Manganese and chromium are also known to compete with iron for absorption in the digestive tract and binding to transferrin, which ultimately disrupts iron homeostasis and may exacerbate iron deficiency anemia [5]. Manganese [18] and chromium [19] are widespread in plant foods, so vegan and vegetarian diets are rich in these elements. However, the possibility of its excessive intake is extremely low [37].

There is evidence that aluminum may be associated with the development of microcytic anemia in patients with chronic renal failure. The mechanism is not well understood, but aluminum is believed to inhibit heme synthesis enzymes (in similar to lead's mechanism) and also to bind to transferrin, interfering with iron transport [4, 27]. There are very few studies in which the status of aluminum among vegans and vegetarians was evaluated, but some investigators showed that vegetarians and vegans consume more aluminum than omnivores [7, 16, 55].

Antitumor therapy with gallium nitrate can cause hypochromic anemia [46]. According to the authors, this may be because gallium can bind to transferrin and thereby disrupt iron metabolism. To date, we haven't found data on the gallium status of vegans and vegetarians.

Conclusion

In clinical practice, therapists often limit themselves to a general blood test with the appearance of anemia symptoms. Microcytosis (decreased MCV) and decreased hemoglobin content in red blood cells (MCH and MCHC) are the reason to diagnose with iron deficiency anemia (IDA) [33]. However, as we see, iron deficiency is not the only cause of hypochromic anemia. This conclusion can only be made after analyzing the ferritin level in the blood [6]. In case if its level is adequate, it makes sense to study the concentrations of copper and lead in the blood and urine, as well as the blood content of ceruloplasmin [2, 10].

Even in the case of IDA, it is advisable to examine the more complete elemental status of the body, since zinc, manganese, chromium, aluminum, and gallium also affect the metabolism of iron. Therefore, iron supplementation may not be enough to treat such patients.

Besides, other elements may also indirectly affect hemoglobin synthesis. For example, Pornprasert et al. found that the residence of anemia patients in regions with excessive fluorine content in the environment may be associated with more severe manifestations of anemia. This can be explained by the fact that excessive fluorine intake can damage the gastrointestinal mucosa and reduce the absorption of nutrients, including iron. At the same time, excess fluorine did not cause anemia in subjects without hematologic disorders [40].

Some elements have the opposite effect. Tammaro et al. conducted oral hyposensitization therapy with low doses of nickel among nickel-sensitized patients and found that all subjects had increased concentrations of hemoglobin in their blood after a year: it confirmed authors' suggestion that nickel deficiency could be associated with low hemoglobin [52]. Cobalt is al-

so known as a hematopoietic inducer and has even been recognized as a dope by the World Anti-Doping Agency (WADA) [48]. Cobalt and nickel stimulate hematopoiesis by modeling hypoxic conditions. They stabilize the hypoxia-inducible factor (HIF), which is an activator of the erythropoietin synthesis [32].

It is also to remember that the clinical picture of IDA can develop due to latent hemolysis or latent blood loss. Isolated therapy with iron may not be enough in these cases, and such patients need etiotropic treatment. Moreover, hypochromic anemia may be genetically determined, such as thalassemia. All of this should be considered when selecting a therapy.

Nutritional factors can affect the risks of other forms of anemia, for example, megaloblastic type. In this case, we talk about normo- or hyperchromic anemia [31]. As for vegans and vegetarians, they may have a higher risk of B12 deficiency anemia [6], as they usually lack this vitamin [42]. On the contrary, folate-deficiency anemia is less common in vegans and vegetarians, as their diet is rich in plant foods (especially leafy vegetables, herbs) and they rarely have folate deficiency [44]. In addition to the typical picture of a general blood test, diagnostic signs of megaloblastic anemia are reduced blood levels of B12 and B9, combined with increased rates of homocysteine and methylmalonic acid [6].

There is a wide variety of anemia: posthemorrhagic, hemolytic, and dyserythropoietic (aplastic) – which may have various causes, including rare mutations [10, 31]. Diagnosis with anemia should include analysis of not only indicators of iron homeostasis, but also the level of other elements, vitamins, and metabolites, which allows to get as close as possible to the true cause of the pathology and conduct the treatment most effectively.

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АССОЦИАЦИЯ МИКРОЭЛЕМЕНТОЗОВ С РИСКОМ РАЗВИТИЯ ГИПОХРОМНОЙ АНЕМИИ У ВЕГЕТАРИАНЦЕВ И ВЕГАНОВ

А.В. Гальченко, А.А. Шерстнева

Гипохромные анемии занимают значительное место в группе алиментарно-зависимых анемий. Основной причиной их развития является дефицит железа, как элемента, входящего в состав гемоглобина. Однако серьезной клинической ошибкой является сведение любой картины микроцитарной гипохромной анемии к железодефициту. Огромное влияние на синтез гема оказывает медь, через регуляцию обмена железа. Таким образом, в организме может быть достаточно железа, но в условиях дефицита меди он не способен встроиться в протопорфирин для образования гема. Встраивание железа в протопорфирин нарушается и при избыточном поступлении в организм свинца. Более серьезная интоксикация этим элементом повышает и гемолиз эритроцитов, тем самым усугубляя течение анемии. На процесс синтеза гема прямо или косвенно влияют и другие элементы: цинк, марганец, хром, алюминий, галлий. Все это обуславливает значительную роль оценки элементного статуса организма при дифференциальной диагностике гипохромных анемий.

Ключевые слова: вегетарианство, веганство, питание, железо, медь, свинец, гипохромная анемия, дифференциальная диагностика анемии.