

VITAMIN D AND MULTIPLE SCLEROSIS

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Abstract

Multiple sclerosis (MS) is the most common autoimmune demyelinating disease of the central nervous system (CNS) - the brain and spinal cord, characterized by the development of demyelination foci scattered in time and space and diffuse changes in brain tissue, which is clinically manifested by multifocal neurological symptoms. MS is one of the severe forms of organic damage to the nervous system, which mainly affects young and working-age people, which leads to a decrease in their quality of life and the development of disability.

Keywords

nutritional behavior, hyperbaric oxygen therapy, genetics, immune response genes, diet, disability, cognitive impairment, vitamin D.

Multiple sclerosis (MS) is a chronic demyelinating disease, which is based on a complex of autoimmune and neurodegenerative processes leading to multiple focal lesions of the central nervous system (CNS), axonopathy, which in turn leads to impaired cognitive functions. Previously, it was believed that 50% of patients lose the ability to walk independently 15 years after the onset of the disease, and currently the average duration of the disease is 20 years or more. It is common knowledge that women are more likely to suffer from many autoimmune diseases. MS is no exception [1]. This fact is associated with the participation of sex hormones and/or sex-linked genes responsible for the increased susceptibility of women to autoimmune diseases. In men, the onset of the disease develops later than in women (on average by 5 years), and coincides with the onset of a natural biological decline in testosterone levels. At the end of the last century, a number of studies were conducted to determine the effect of pregnancy on the course of MS [2, 4]. A more positive effect of pregnancy on the course of MS was noted in patients with relapsing-remitting MS than in patients with a secondary progressive course, which is most likely due to the age of the patients and their reproductive potential at the time of pregnancy. It was found that during pregnancy, autoimmune damage to the central nervous system subsides, which is confirmed by MRI results: a decrease in the number of lesions during the second half of pregnancy and a return of disease activity in the first month after birth in the form of the appearance of new lesions. The fetus, which is essentially an allogeneic transplant for the mother's body and carries the father's antigens, secretes cytokines that reduce the production of anti-inflammatory cytokines by the mother's body and "switch" the balance of cytokines towards anti-inflammatory ones [2, 3, 4]. Despite the progress achieved in treatment, MS remains one of the socially significant problems in neurology: people of young and working age are susceptible to this disease, which often leads to disability, which determines the high medical and socio-economic significance of the problem [1]. According to European and American organizations, MS is the most expensive chronic neurological disease (per patient over a lifetime) for the state and private insurance companies. The leadership of MS in these indicators is associated with the early onset of the disease, the significant life expectancy of patients, and the high cost of modern methods

of diagnosis and treatment of patients with this nosology [8]. Today it is generally accepted that MS is a multifactorial disease. Despite the active research and study of MS in recent years, the etiology and pathogenetic mechanisms of the development of the disease still remain unclear. It is known that MS is most common in areas with a cool and humid climate, and therefore the connection between the incidence of MS and such environmental factors as: the composition of water and soil (lack of microelements in them - cobalt, copper, manganese, zinc) is still being discussed, iodine); food (eating large amounts of animal fats); illumination (insolation). Population-based studies were conducted in a number of countries with a predominantly cold climate (Sweden, England, Scotland and other countries), based on these studies it was noted that patients with MS are more often born in months with the least number of sunny days. It was also noticed that the frequency of MS increases with distance from the equator. There is a hypothesis that latitude influences the risk of developing MS through the level of insolation and serum levels of vitamin D. In a number of studies, it was observed that people born in the spring have a higher risk of developing MS than people born in the fall. A study from Australia shows that the risk of developing MS is lower among those who spent more time in the sun during holidays and weekends as children than those who were protected from the sun. Much attention is paid to the level of vitamin D in the blood of patients with MS. From 90 to 100% of vitamin D is produced endogenously under the influence of insolation, which is maximum in countries of Africa and Asia, where the incidence of MS is minimal. Food products contain very little vitamin D (the only exception is fish oil, which "we were given as children"). Fatigue and depression are common symptoms of MS, and these are also associated with vitamin D. A 2010 study on fatigue and depression in MS found that vitamin D levels were negatively correlated with depression levels. An interesting fact is that, however, among the Eskimos and indigenous peoples of the North, despite the distance from the equator, MS does not occur, which is apparently due to genetic factors and the eating behavior of this population - the constant consumption of fish and fish oil - one of the key points in the diet patients with MS [3]. Vitamin D is a group of biological substances that play a key role in calcium-phosphorus metabolism, as well as participate in other metabolic processes, including the regulation of the immune system. About 80% of the vitamin D reserve is formed in the skin under the action of ultraviolet rays (while 7-dehydrocholesterol is converted into cholecalciferol), and the remaining 20% is obtained by the body with food (cholecalciferol – with food of animal origin, ergocalciferol – with food of plant origin). Ergo- and cholecalciferol are biologically inert, and 2 stages of hydroxylation must occur to convert them into the active form. First, calcidiol is formed under the action of liver 25-hydroxylase [25 (OH)D], which is an indicator of the status of vitamin D in the body. Then, under the action of 1 α -hydroxylase of the kidneys or immune cells, it is converted into calcitriol [1,25 (OH)D] is an active metabolite that binds to the vitamin D receptor and causes all the effects of this group of substances. The fact that vitamin D receptors are present in cells of the immune system suggests the regulatory role of vitamin D on the body's immune response. There are more modern prospective studies of the risk of developing MS, which already take into account the concentration of 25(OH)D in the blood serum of patients with MS. For example, when studying the health of US military personnel, a case-control study was conducted. It obtained the following results: on average, the level of vitamin D in the blood serum of people of the Caucasian race is higher than that of representatives of the black race, but the risk of MS in the former is higher, which is associated with a greater genetic predisposition [6]. There are other data as well. In a case-control study conducted in Germany among blood donors, the following results were obtained: the level of vitamin D in the serum of people who subsequently developed MS significantly gradually decreased before the clinical manifestation of the disease. At the same time, 2 years before the onset of symptoms, the serum level is 25 (OH)D did not significantly differ from the group of healthy volunteers. Thus, this study suggests that a decrease in vitamin D in the blood is

more likely to be associated with the development of the disease itself, rather than a risk factor for its development. This decrease seems to be associated with a change in metabolism, because patients with MS are characterized by the phenomenon of "consumption" of vitamin D: with equal intake, their blood levels are significantly lower than in healthy volunteers [7]. There are also suggestions in the medical literature that the risk of developing MS is primarily affected by vitamin D deficiency in the mother during pregnancy, as well as in childhood. The study [6], which is essentially a continuation of Nurses' Health Study II, can speak in favor of this theory. It showed a reduced risk of MS for nurses whose mothers drank more than 3 glasses of milk per month and predictively had higher levels of vitamin D in their blood. But this study has the following limitations: firstly, it was a questionnaire, and the questionnaires were filled out after a long period of time (after more than 20 years), and secondly, it was retrospective in nature. In another case-control study [7], the following results were obtained: after an honest analysis, when divided into quintiles by serum vitamin D, there was no increase in risk for the lower quintiles, if we take the risk in the upper quintile as a unit. But the authors found statistical reliability: if we take as a unit the risk in terzil, which corresponds to vitamin D deficiency, then in terzil, which corresponds to a pronounced vitamin D deficiency, the risk is significantly higher. But at the same time, it turns out that the risk in the tercile, which corresponds to vitamin D deficiency and norm, is also higher, although unreliably. This part of the result slightly contradicts the data on reducing the risk of MS with an increase in serum vitamin D concentration. Also, the data from the already mentioned study [3] indicate that there is no connection between the level of 25(OH)D in the mother's blood and the risk of developing MS in the fetus in the future. If we move on to more reliable studies, then it is worth paying attention to the published meta-review [8]. It shows that taking vitamin D3 (cholecalciferol) does not affect the recurrence rate, disability, or disease activity. It is also noted that to date, all the evidence is of very low quality and the conclusions are based on a small number of studies. Separately, it is worth considering the results of three major studies: SOLAR [5], CHOLINE [6] and SOLAR [4]. The first two randomized trials compared groups of patients taking high-dose cholecalciferol (14,000 IU per day - SOLAR; 100,000 IU per week - CHOLINE) + IFN- β or placebo + IFN- β . The SOLAR study did not have an effect on the activity of the disease according to the NEDA-3 criterion, but there were improvements in the radiological picture. The CHOLINE study showed a decrease in the number of new T1 foci and the total volume of T1 foci, while there were no differences in the number of T2 foci and foci accumulating gadolinium. There were decreases in the assessment of disability on the disability scale, but no differences were found on the quality of life scales (EQ-SD-3L or PASAT-3). In conclusion, this work makes the statement that there is no effect of taking cholecalciferol in patients with low levels of 25(OH)D in the blood for the number of relapses of the disease (the level of reliability of evidence is 2). In the SOLAR study, patients first took cholecalciferol 7000 IU per day for 4 weeks, and then 14,000 IU per day for up to 48 weeks or a placebo. All patients took IFN- β . There was an imbalance in the control group towards proinflammatory cytokines compared with the vitamin D3 group, but no other changes in the immune status were detected. Thus, the authors conclude that D3 has a minimal effect on the immune system, but do not deny it. As a separate point, I would like to note that the prospects for the treatment of MS with high doses of vitamin D3 (cholecalciferol), which have been made public in the media, have not yet been confirmed in the course of research. Moreover, there are reports of patients who themselves [3], having received information on the Internet, or after private consultations with doctors, promoted this method of treatment at home (in Brazil) [4], took high doses of cholecalciferol (more than 50,000 IU per day). These patients showed no signs of slowing down the progression of the disease, but adverse events such as fatigue, chronic kidney disease, severe gastropathy, seizures, nephrolithiasis and nephrocalcinosis appeared on the background of hypercalcemia in the range of 3.29–4.2 mmol/l [4],

while the vitamin D level was about 150 ng/ml. In addition, it is reported that taking high doses of cholecalciferol is associated with the risk of celiac disease [5]. Based on these data, it is necessary to conclude about the extreme danger of taking high doses of cholecalciferol. Conclusion To date, there is no clear evidence linking vitamin D deficiency with the risk of developing MS. Low vitamin D levels in people with MS may be associated with a more severe course of the disease. There is also no evidence of a significant improvement in the course of MS when relatively high doses of vitamin D are added to standard IFN- β therapy. Despite such conclusions, healthy people should adhere to the recommendations of the US Institute of Medicine [6] and maintain a level of 25(OH)D in the blood at the level of 50-125 nmol/l (the level of reliability of evidence is 1, class A recommendations), which usually requires consumption of 600-2000 IU per day. The recommended daily dose according to Russian recommendations is 600-800 IU.

References

1. Boyko A, Smirnova N, Petrov S, Gusev E. Epidemiology of MS in Russia, a historical review. *Mult Scler Demyelinating Disord.* 2016; 1: 1–6. DOI: 10.1186/s40893-016-0016-9
2. Dendrou CA, Fugger L, Friese MA. Immunopathology of multiple sclerosis. *Nat Rev Immunol.* 2015; 15: 545–58. DOI: 10.1038/nri3871
3. Beckmann Y, Türe S, Duman SU. Vitamin D deficiency and its association with fatigue and quality of life in multiple sclerosis patients. *EPMA Journal.* 2020;11: 65–72. DOI: 10.1007/s13167-019-00191-0
4. Tarlinton RE, Khaibullin T, Granatov E, et al. The interaction between viral and environmental risk factors in the pathogenesis of multiple sclerosis. *Int J Mol Sci.* 2019; 20 (2): 303. DOI: 10.3390/ijms20020303
5. Dobson R, Giovannoni G. Multiple sclerosis – a review. *Eur J Neurol.* 2019; 26 (1): 27–40. DOI: 10.1111/ene.13819
6. Thompson AJ, Baranzini SE, Geurts J, Hemmer B. Multiple sclerosis. *Lancet.* 2018; 391 (10130): 1622–36. DOI: 10.1016/S0140-6736(18)30481-1
7. Sospedra M, Martin R. Immunology of Multiple Sclerosis. *Semin Neurol.* 2016; 36 (02): 115–27. DOI: 10.1055/s-0036-1579739
8. Hupperts R, Smolders J, Vieth R, et al. Randomized trial of daily high-dose Vitamin D3 in patients with RRMS receiving subcutaneous interferon β -1a. *Neurology.* 2019; 93 (20): E1906–16. DOI: 10.1212/WNL.0000000000008445
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