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Review

ROLE OF DIET AND SUPPLEMENTATION WITH OMEGA-3 POLYUNSATURATED FATTY ACIDS FOR MANAGING CHRONIC FATIGUE IN PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS

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Summary

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system (CNS) with unclear and multifactorial etiology, variable clinical symptoms with different severity, and treatment with limited efficacy. Authors conclude that the immune system has a role in pathogenesis, and many modern therapies target the immune system. Among clinicians, it is accepted that not every patient will progress in the same way, and there is high variability between clinical courses of MS in different patients.

Modern therapies have shown to reduce new lesions and clinical relapses but lack effectiveness at halting underlying neurodegeneration at lesions, the localized inflammation on a small scale, chronic demyelination, and axonal and neuronal damage. Dietary metabolites have far-reaching and systemic effects. It has been suggested that diet can play an essential role in helping to modify immune system function to promote regulation as opposed to inflammation. Polyunsaturated fatty acids decrease inflammation through conversion into anti-inflammatory prostaglandins E1 and E2, which affect cytokine production, leukocyte migration, and other immune system components. The Mediterranean style diet is a diet low in saturated fats, high in polyunsaturated and monounsaturated fats, rich in fruits and vegetables, and low in processed foods (low salt content). Eating a Mediterranean-style diet can help reduce fatigue (as reported by patients) and change the clinical course favorably.

Keywords: relapsing-remitting multiple sclerosis, Mediterranean diet, chronic fatigue, polyunsaturated fatty acids, interleukin 17

Introduction

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system (CNS) with unclear and multifactorial etiology, variable clinical symptoms with different severity, and treatment with limited efficacy. It is generally characterized by systemic inflammation and activation of autoimmune

processes in the human body leading to demyelination of the white matter in the CNS with or without the formation of plaques, gliosis, and axonal damage. The clinical manifestation of neurological deficits may be more or less severe, and the process dynamics are generally unpredictable [1-3].

Clinical presentation of MS

The typical onset of the disease is at a young age, with a peak in the most active third decade of life. The increasing incidence of MS, it's debatable etiopathogenesis, and the chronic clinical dynamics with unpredictable rates of disability dictate the socio-medical impact of the disease worldwide [1]. The study emphasizes the social significance of the scientific problem in our country. According to global data from 2019, disability-adjusted life expectancy (DALYs) in Bulgarian patients with MS increased by 8.1% from 1990 to 2016 [4].

Relapsing-remitting MS (RRMS) is the most common form of the disease, diagnosed in 85% of patients with MS. In Bulgaria, the number of people living with RRMS is about 6 000. The attacks of RRMS have apparent neurological symptoms that develop slowly within a few weeks. No progression of the disease is observed between attacks. About 62% of the affected individuals have a disability of a varying, rather moderate, severity [1, 2].

Innovative treatment approaches, such as disease-modifying therapy, modern neurosurgical techniques like stereotactic surgery, and minimally invasive CNS surgery with navigation and deep brain stimulation, have been investigated to manage general symptoms and detect CNS lesions [5-7]. Modern therapies have been shown to reduce new lesions and clinical relapses. However, such therapies lack effectiveness at halting underlying neurodegeneration at lesions, the localized inflammation on a small scale, chronic demyelination, and axonal and neuronal damage. It is suggested that in these lesions, dietary factors can reduce CNS inflammation, combat oxidative stress or protect mitochondria and may help prevent chronic demyelination and axonal and neuronal damage [8-11].

Nutrition and supplementation in MS

Omega-3 fatty acids are a group of nine polyunsaturated fatty acids (PUFAs) that are not synthesized in the human body. Three PUFAs are essential for human nutrition and are recommended in the main diets of MS: alpha-linolenic (ALA), eicosapentaenoic (EPA, C20: 5n3), and docosahexaenoic DHA, C22: 6n3) fatty acids [12-18]. What they have in common is the presence of a double carbon bond in the omega-3 (ω-3) position in their molecular structure, which unites them into a separate group [19]. Polyunsaturated fatty acids are found in fish, walnuts, and flax seeds; EPA and DHA are found in fish; ALA is found in plant-based foods. Polyunsaturated fatty acids are concerned with decreasing inflammation through conversion into anti-inflammatory prostaglandins E1 and E2, which, in turn, affect cytokine production, leukocyte migration, and other immune system components [8, 9]. Nuts are also high in resveratrol - an anti-fungal compound suggested to affect positively neurodegenerative diseases with inflammation [9]. Fish oil and the Mediterranean diet are rich in essential omega-3 PUFAs. International studies have shown that they have a proven anti-inflammatory effect by several main mechanisms [20-23]:

- Replacement of arachidonic acid (AA) in leukocyte membranes and limited production of pro-inflammatory eicosanoids.
- Activation of biomarkers with less inflammatory action than the substances obtained from the transformation of n-6 polyunsaturated fatty acids;
- Metabolism to a series of mediators involved in immune processes and helps to control inflammatory reactions (resolvins and protectins).
- Another possible mode of action of these dietary components is the promotion and support of remyelination; this process is highly variable between individuals and reported by preclinical studies on experimental animals. The adult human brain contains oligodendrocyte precursor cells capable of remyelination, but they are largely inhibited. Medical therapies to switch these cells on are yet to be successfully translated from animal studies to humans.

Immunity and inflammation in MS

The role of pro-inflammatory and anti-inflammatory cytokines (IL-17A) secreted by different populations of immunocompetent cells in regulating central autoimmune processes in MS is highly debatable. There are reports that the influence of autoreactive CD4 + T lymphocytes of the Th1 phenotype on the development of the autoimmune cascade is critical. Recent studies have also discussed the involvement of B lymphocytes in the generalized pathogenetic galaxy. The pro-inflammatory effect of the activated Th17 cell subpopulation in general and central immune-mediated reactions is somewhat elucidated. Studies in experimental animals with EAE have established the ability of Th17 lymphocytes to independently induce disease, suggesting that they alter the permeability of the blood-brain barrier with a subsequent intense influx of a large number of antigen-specific cells [24-29].

Chronic fatigue in MS

The factors contributing to the symptoms of chronic fatigue, mood swings, and cognitive impairment during the course of the disease have not been sufficiently studied and elucidated. [20, 28, 30-35] Some of the pilot studies conducted in 2008-2016 on the application of stabilized enteral formulas containing fish oil and enriched with EPA and DHA for long-term enteral nutrition of hospitalized patients with critical illnesses reported proven benefits of the intervention by reducing mortality, reducing the risk of developing new tissue and organ damage, reduced mechanical ventilation time and reduced hospital stay. Other studies have administered only fish oil via enteral bolus during the same period, which did not show any added benefits [19]. In a 2008 meta-analysis (Pontes-Arruda et al.), the authors have reported a proven positive effect of PUFAs-containing food supplementation on inflammation, immune parameters, and organ damage in patients with sepsis. They emphasise that the nature of interventions (nutrition or supplementation), their dosage, the route of administration, and the frequency of supplementation in the design of such studies need further clarification [8, 9, 31-33].

Diet and supplementation in MS

Although (unlike conventional drugs), pharmaconutrients are rarely subject to precise pharmacokinetic (PK) analysis in preclinical and clinical studies, EPA and DHA PK have been studied in healthy volunteers (Power et al. 1998). However, full extrapolation of these data is controversial due to dysfunction of various organs, changes in gastrointestinal motility, abnormal liver and kidney function, and many other disease-specific factors [10, 11, 14, 34, 37-40]. Moreover, there are few well-designed studies in this direction in CNS diseases. It is biologically plausible to expect individual differences in the movement and behavior of enteral nutrients, including EPA and DHA, in patients with chronic autoimmune and brain diseases, including MS, given the as yet unexplained changes in brain metabolism and the mobile cascade of significant pro-inflammatory, immune and oxidative biomarkers. [30, 41-46]. To the best of our knowledge, studies with similar designs have not been conducted in our country. However, there is convincing evidence from leading Bulgarian researchers on the increasing incidence of chronic fatigue, leading to impaired functioning of patients with RRMS. Such impaired functioning has been reported in cases of disease-modifying therapy and cases when, for various good reasons, the recommended drug treatment is not prescribed or discontinued. [2, 3, 28, 47-49] Physicians know that some patients voluntarily withdraw from therapy and turn to non-therapeutic methods and advice from non-specialists in neurology and nutrition. Such practices add to the risk of poor disease control.

National guidelines on the management of MS

The current National Consensus on the Diagnosis and Treatment of MS from 15 March 2021 states that therapy's most important therapeutic goal is to delay and reduce disability in the long run [1]. The occurrence of neutralizing antibodies even to humanized monoclonal antibodies used in standard therapeutic regimens as a reason for the insufficient effectiveness of some biological drugs is analyzed. The frequency and severity of adverse drug reactions and toxicity of common treatments that may require discontinuation of drug therapy are also discussed. A hygienic-

dietary regime with reduced salt and animal fats in the diet is recommended, at the expense of food sources supplying PUFA and vitamin D. For patients with symptoms of chronic fatigue, national and international authorities recommend lifestyle changes such as aerobic activity, physiotherapy, behavioral therapy and other methods along with the disease-modifying therapy. Foods rich in cellulose fiber, hydration, and hot drinks are strongly encouraged if gastrointestinal problems occur. Emphasis is placed on educating and encouraging patients to follow an appropriate diet and avoid alternative therapies.

Conclusion

This review is based on current international and national scientific evidence and recommendations pointing to the need for expanded research in various aspects of MS, including modification of patients' diet and lifestyle. Given the undeniable socio-medical significance of the disease, we believe that the results of this project will be valuable for a modern and professional outline of additional-to-treatment approaches to Bulgarian patients living with MS. It may also enrich our practical experience with broader opportunities for optimizing the quality of life of people suffering from RRMS in actual clinical conditions.

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