Nutritional intervention as an essential part of Multiple Sclerosis treatment?

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Review

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Short title: Diet in MS treatment

Summary

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system. In addition to the genetic, epigenetic and immunological components, various other factors e.g. unhealthy dietary habits play a role in the MS pathogenesis. Dietary intervention is a highly appealing approach, as it presents a simple and relatively low risk method to potentially improve outcomes in patients with brain disorders in order to achieve remission and improvement of clinical status, well-being and life expectancy of patients with MS.

The importance of saturated fat intake restriction for the clinical status improvement of MS patients was pointed for the first time in 1950s. Recently, decreased risk of first clinical diagnosis of CNS demyelination associated with higher intake of omega-3 polyunsaturated fatty acids particularly originating from fish was reported. Only few clinical trials have been performed to address the question of the role of dietary intervention, such is e.g. low saturated fat diet in MS treatment. This review summarizes current knowledge about the effect of different dietary approaches (diets low in saturated fat and dietary supplements such as fish oil, lipoic acid, omega-3 polyunsaturated fatty acids, seeds oils, high fiber diet, vitamin D, etc.) on neurological signs, patient's well-being, physical and inflammatory status. So far the results are not conclusive, therefore much more research is needed to confirm and to understand the effectiveness of these dietary interventions in the long term and well defined studies.

Key words: Multiple sclerosis – neuroinflammation – diet – saturated fatty acids – unsaturated fatty acids

Abbreviations

BBB	blood-brain-barrier
CAM	complementary and alternative medicine
cAMP	cyclic adenosine monophosphate
CNS	central nervous system
DHA	docosahexaenoic acid
EAE	experimental autoimmune encephalomyelitis
EDSS	extended disability status score
EPA	eicosapentaenoic acid
FCD	first clinical diagnosis of CNS demyelination
GABA	gamma-aminobutyric acid
ICAM	intercellular adhesion molecule
IFN	interferon
IL	interleukin
LA	linoleic acid
LDL	low-density lipoprotein
MRI	magnetic resonance imaging
MS	multiple sclerosis
MUFA	monounsaturated fatty acid
PPAR	peroxisomal proliferators-activated receptor
PUFA	polyunsaturated fatty acid
SAFA	saturated fatty acid
SCFA	short-chain fatty acid
TGF-β	transforming growth factor β
TNF	tumor necrosis factor
VCAM	vascular cell adhesion molecule

Review

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory disease affecting the central nervous system (CNS), leading to neurodegenerative processes in the nervous system, characterized by inflammation and myelin loss. The disease typically manifests as motor impairment, visual disturbances, or sensory problems. Other symptoms include, pain, fatigue and cognitive impairment (Dendrou *et al*. 2015). MS usually develops in young adults; women are more likely to be affected. There are two main types of the disease 1) relapsing-remitting MS (85%); with inflammation and demyelination as the primary pathology and 2) primary-progressive MS (15%); with neurodegeneration – axonal degeneration as the primary pathology (Storoni and Plant 2015).

The prevalence of MS is higher in developed countries (Evans *et al.* 2013); the highest in the Orkney Islands, which belong to Scotland (250 per 100 000), Norway (208 per 100 000 in 2013; the reported prevalence of MS in Norway has increased 10-fold during last 8-9 decades (Grytten *et al.* 2015); followed by Hungary (176 per 100 000), Slovenia (150 per 100 000), Germany (149 per 100 000), USA (135 per 100 000), Canada (149 per 100 000), and Czech Republic (130 per 100 000). MS is very common in Scandinavia, northern and middle Europe (80-100 per 100 000), extremely rare in Japan (2 per 100 000) and is almost unknown in the Indian subcontinent (Browne *et al.* 2014; Kingwell *et al.* 2013).

The pathogenesis of MS is complex and multifactorial (Wu *et al.* 2016). In addition to the genetic, epigenetic and immunological components, various other environmental factors may play a role in the development of MS (brain injury, viral infection i.e. Epstein-Barr virus, nutrition - so-called Western diet, physical inactivity, obesity in childhood and adolescence, smoking, low vitamin D level, etc.) (Dos Passos *et al.* 2016; Pierrot-Deseilligny and Souberbielle 2017). On the other hand, physical exercise, assumed „healthy diet“ and restoration of optimal concentrations of vitamin D have an antiinflammatory effect and may ameliorate the course of many chronic inflammatory diseases, such as MS (Marck *et al.* 2016). Meta-analysis of epidemiological studies has demonstrated a relation between MS mortality and dietary fat, where intake of saturated fatty acids, mainly in animal fat products correlates positively with MS mortality (Esparza *et al.* 1995). An increased risk of MS was found to be associated with high energy and animal food intake (Ghadirian *et al.* 1998). The same study also revealed a protective effect of other nutrients, including vegetable protein, dietary fiber, cereal fiber, vitamin C, thiamine, riboflavin, calcium and potassium. In contrast, another study found no associations between intake of fruits and vegetables, multivitamins, vitamins C and E, and the risk of MS in women (Zhang *et al.* 2001).

It is known that the so-called Western diet contains, besides others, too much fat, especially saturated fatty acids (SAFA). Data from Food and Agriculture Organization of the United Nations indicate that during the last 30 years fat from all sources consumed by Americans increased from 119 g per capita per day to 155 g per capita per day (85 g from monounsaturated fats (MUFA)), representing 42% of total energy intake. Further findings reported that the US dietary pattern changed, including more saturated fats as a result of broad availability of fast foods (Wilczynska-Kwiatek *et al.* 2010). In French adults the mean total fat intake per capita per day was 94.1 g in men (36.3% of total energy intake) and 73.4 g in women (38.1%), respectively (Astorg *et al.* 2004).

The current recommended dietary allowance for fat intake for adults varies from 20 to 35% of total daily calories according to the World Health Organization, Food and Agriculture Organization of the United Nations, the European Food Safety Authority or dietary guidelines for Americans. Intake of SAFAs should not exceed 10% of total daily caloric intake. The recommended range for polyunsaturated fatty acids (PUFAs) is 6-11% of total daily caloric intake (FAO 2010) (Table 1).

Diet	**Total fat/day**	**SAFAs/day**	**PUFAs/day**
2000 kcal/day	44 - 78 g	< 22 g	13 - 24 g
2500 kcal/day	56 - 97 g	< 28 g	17 - 31 g

Table 1. The recommended fat intake for adults (FAO 2010).

On the other hand, south Asian diet (India, Korea, Thailand, etc.) is low in SAFAs and high in PUFAs (especially omega-6), and Japanese consume large amounts of omega-3 fatty acids, mostly from sea food. Other contributing factor is high intake of vegetables and lots of plant food rich in dietary fibers. Therefore, the question arises, whether these dietary habits can explain the rare prevalence of MS in these populations, besides the genetic and epigenetic factors.

Lot of patients with MS use special diet and dietary supplements proposed by complementary and alternative medicine, mainly due to unsatisfactory effect of the conventional therapy or its side effects.

Fat intake and neuro-inflammation

Myelin around axons, its lipid composition, and membrane lipid morphology are affected during the progression of neuroinflammatory and neurodegenerative diseases. High fat diet induces markers of brain inflammation, with proinflammatory actions in cerebral cortex and hippocampus.

Cholesterol is an essential component of cellular and myelin membranes of neuronal cells in mammals. In a comprehensive review (Zhornitsky *et al.* 2016), the relationship between levels of cholesterol and markers of cholesterol turnover in circulation and/or cerebrospinal fluid and MS outcomes was discussed. It was suggested that cholesterol and related molecules might be potentially used as markers of the disease activity, of the treatment efficacy or as a new therapeutic target. Increased levels of circulating total cholesterol, LDL-cholesterol, apolipoprotein B and oxidized LDL are associated with adverse disease outcomes. Since the metabolic and vascular comorbidities, such as atherosclerosis, hypertension and obesity, including hypercholesterolemia, are associated with increased risk of developing MS and its rapid progression, the causal relationship between high cholesterol levels and MS outcomes needs to be elucidated (Zhornitsky *et al.* 2016).

Increased intake of certain SAFAs and linoleic acid (LA, 18:2, n-6), introduction of industrially produced *trans* fatty acids into food chain, and reduced intake of omega-3 fatty acids (notably alpha-linolenic acid (18:3, n-3) from vegetable sources) might have adverse health effects (Blondeau *et al.* 2015; FAO 2010; Sala-Vila *et al.* 2016). Omega-3 fatty acids are a family of PUFAs, the parent omega-3 fatty acid is 'the essential fatty acid', the alpha-linolenic acid (18:3, n-3), which must be supplied by diet and can be found in nuts and seeds – flax, hemp, poppy, soybean and their oils. The source of omega-3 fatty acids, eicosapentaenoic acid (EPA; 20:5, n-3) and docosahexaenoic acid (DHA; 22:6, n-3) is fish (e.g. salmon, mackerel, herring and sardine), their synthesis from alpha-linolenic acid in humans is limited (Fetterman and Zdanowicz 2009). DHA crosses the blood–brain barrier and, along with arachidonic acid, is a major component of neuronal cell membranes (Lim and Suzuki 2000). EPA can be converted to prostaglandin I3 and E3, thromboxane A3 and leukotriene B5, and therefore has immunomodulatory capacity, acting as an anti-inflammatory agent (Calder 2002; Fetterman and Zdanowicz 2009). PUFAs (in particular DHA and EPA) have neuroprotective action (Das 2001b; Das 2002; Lauritzen *et al.* 2000) and inhibit the production of IL-1, IL-2, and TNF (Kumar and Das 1994; Kumar *et al.* 1992)**.** Finally, both EPA and DHA can form new anti-inflammatory bioactive molecules, called resolvins, protectins, and maresins, which are able to reduce cellular inflammation and inflammatory pain (Hong and Lu 2013; Serhan *et al.* 2015; Xu *et al.* 2010). DHA is present at

high concentration in the brain and its level decreases dramatically in MS patients (Nightingale *et al.* 1990). On the basis of its anti-inflammatory and neuroprotective action, fish oil supplementation was found to be highly effective in reducing the levels of cytokines and nitric oxide in patients with relapsing-remitting MS under treatment with IFN-β (Ramirez-Ramirez *et al.* 2013).

Further, n-3 fatty acids (especially EPA and DHA) enhance the production of transforming growth factor-β (TGF-β), which shows anti-inflammatory properties (Das 1993; Das 1995; Fernandes *et al.* 1998; Newman 1990). In chronic silent MS, TGF-β transcription was reported to be increased, reflecting gliosis or suppression of the inflammatory response (Lock *et al.* 2002).

Lipoic acid (containing sulphur) is an antioxidant and therefore important for normal function of mitochondria. It has been shown to be an effective treatment for animal model of MS – the experimental autoimmune encephalomyelitis (EAE) (Marracci *et al.* 2002; Morini *et al.* 2004; Schreibelt *et al.* 2006). Lipoic acid suppresses EAE by interfering with trafficking of encephalitogenic T cells into the spinal cord. Lipoic acid has immunomodulatory and antiinflammatory properties, stabilizes the integrity of the blood–brain barrier (BBB) and stimulates the production of cAMP and the activity of protein kinase A (Salinthone *et al.* 2010). Immunomodulatory effects of lipoic acid involve several mechanisms, e.g. inhibition of the expression of the intercellular and vascular cell adhesion molecules (ICAM-1 and VCAM-1) by CNS endothelial cells (Marracci *et al.* 2002; Marracci *et al.* 2004; Morini *et al.* 2004). Lipoic acid is a nutritional supplement with a variety of biological effects as antioxidant and is approved for treatment of peripheral neuropathy (Ziegler *et al.* 1999).

Neuronal cells represent insulin independent tissue in terms of using glucose as a fuel, however, brain is rich in insulin receptors (Hill *et al.* 1986). Insulin has many functions in the brain; insulin itself participates in neuronal growth and differentiation, neurotransmitter release, and synaptic plasticity (Bruning *et al.* 2000; Rulifson *et al.* 2002). SAFAs can make the cell membrane rigid, reduce the number of insulin receptors and the affinity of insulin to its receptors. So, an important function of PUFAs in the brain is to ensure the presence of adequate number of receptors for insulin and neurotransmitters for their appropriate actions. Moreover, insulin enhances the activities of desaturases (Das 2005; Das 2007) and thus increases the formation of n-6 and n-3 long-chain PUFAs from their respective precursors. Insulin stimulates the endothelial nitric oxide (eNO) synthesis (Kuboki *et al.* 2000), modulates immune response, and has anti-inflammatory actions (Das 2001a; Sun *et al.* 2014).

Balance between PUFAs and SAFAs in the cell membrane is critical to the function of insulin (Das 1994). Appropriate amounts of PUFAs and, consequently, insulin receptors in the brain are critical to the health of brain neurons. Thus, when adequate amounts of PUFAs (especially DHA) are incorporated into the neuronal cell membranes, it may protect neurons from the cytotoxic action of TNF by its direct neuroprotective action and its enhancement of the number of insulin receptors because insulin can silence the neurotoxic signal of TNF. Recently, epidemiological studies on neurodegenerative disorders have evaluated the beneficial effect of PUFAs on multiple sclerosis (Wergeland *et al.* 2012).

In our previous study (Penesova *et al.* 2015), we found signs of insulin resistance in newly diagnosed, untreated patients with MS with low Expanded Disability Status Scale (EDSS) score (1.1 ± 0.7). Our data further suggest that chronic inflammation, physical inactivity, autonomous nervous system dysfunction, changes in incretin or adipokine secretion are not likely to be involved in the development of insulin resistance in MS patients. Gong *et al.* (Gong *et al.* 2008) hypothesized that in vivo insulin deficiency may be a novel etiological cause of demyelinating disease and thus improving the insulin sensitivity represents the novel therapeutical strategy for remyelination and neuronal repair. There are few running studies with peroxisomal proliferators-activated receptor gamma (PPAR-γ) agonists (a common antidiabetic drug) in MS (Bright *et al.* 2008). However future human trials will probably confirm the safety and efficacy of PPAR agonists for MS treatment.

Hoare et al (Hoare *et al.* 2016) examined the association between usual fat intake (total, SAFA, MUFA, PUFA, omega-3 and omega-6) and risk of a first clinical diagnosis of CNS demyelination (FCD) in a multi-centre incident case-control study in four regions of Australia during 2003-2006. Dietary data were collected from patients with FCD and matched controls using a validated food frequency questionnaire. They found that there was a significant decrease in FCD risk with higher intake of omega-3 PUFA, particularly that from fish sources. There was no evidence to indicate that the intake of other types of dietary fat or fat quantity in the 12 months prior diagnosis was associated with an altered risk of FCD.

In a double-blind and randomized study, no differences were observed between MS patients and healthy controls with regard to fat malabsorption (Wong *et al.* 1993). Nevertheless, there were deficiencies of essential PUFAs (i. e. PUFAs of the n-3 and n-6 series) in both plasma lipids and erythrocytes of MS patients (Cunnane *et al.* 1989; Holman *et al.* 1989; Cherayil 1984). Plasma LA (18:2, n-6) was normal, *gamma*-linolenic acid (18:3, n-6) was increased in MS patients, but subsequent n-6 acids were subnormal, indicating impairment of chain elongation (Holman *et al.* 1989). In addition, the content of all n-3 fatty acids was subnormal

and PUFA deficiency was compensated mass-wise by an increase in saturated fatty acids concentrations in plasma. Fatty acids levels in red blood cells and adipose tissue change more slowly and persist longer than in serum, and therefore relate more likely to long-term changes in fatty acids levels or metabolism, rather than reflecting dietary alterations. In red blood cells of mild inactive MS patients, there was a significant reduction in EPA (20:5, n-3), and an increase in dihomo-*gamma*-linolenic acid (20:3, n-6) and stearidonic acid (18:4, n-3) (Nightingale *et al.* 1990). No detectable EPA levels in the adipose tissue of MS patients and healthy individuals could be observed. However, whereas in MS patients DHA (22:6, n-3) was not detectable, 40% of healthy controls had significant levels. No reduction in LA was observed in red blood cells or adipose tissue of MS patients (Nightingale *et al.* 1990). In MS plaques, the lipid and fatty acid composition appears to be altered (Wilson and Tocher 1991). The cause of these PUFA deficiencies is not entirely clear and may involve metabolic and nutritional alterations. Long chain n-3 fatty acids such as EPA and DHA are important in the development of the central nervous system, have anti-inflammatory and neuroprotective effects and their decreased levels may be relevant to the pathogenesis and treatment of MS.

The role of dietary habits in neurodegeneration

Dietary habits and especially intake of fatty acids have been suggested as a possible environmental factor affecting risk and progression of MS. First studies on the effect of dietary fat on MS risk from 1950 (Swank 1950) attributed higher incidence of MS in inland farming communities compared to coastal regions of Norway to dietary habits (high content of animal and dairy saturated fat in inland and higher content of fish on the coast).

Based on this observation, a diet with a very low intake of SAFAs for patients with MS was proposed (Swank 1950). Restricting saturated fat intake induced remission and improvement of the disease and showed a marked beneficial effect on the well-being and life-expectancy of patients with MS (Swank 1950; Swank and Dugan 1990; Swank and Goodwin 2003a; Swank and Goodwin 2003b). Patients with actual saturated fat intake of <20g per day were almost free of MS and showed fewer deaths that could be attributed to MS compared with much worse prognosis in those who consumed >20g of saturated fat per day.

Mounting evidence indicates that nutrition can play an important role in MS, however the MS therapy is not currently combined with any dietary and/or lifestyle recommendations.

There have been a number of studies reporting the prevalence of complementary and alternative medicine (CAM) use by MS patients, with a quite broad range of 33–70% (Berkman *et al.* 1999; Leong *et al.* 2009; Marrie *et al.* 2003; Nayak *et al.* 2003; Page *et al.*

2003; Schwartz *et al.* 1999; Schwarz *et al.* 2008; Stuifbergen and Harrison 2003; Yadav *et al.* 2006; Masullo *et al.* 2015). The most prevalent types of CAM are vitamins/minerals, non-vitamin and non-mineral natural products, relaxation techniques, and special diet. Regarding diet, the median percent of calories from fat (37%) and saturated fat (12%) were higher than current recommendations, while dietary fiber intake met only 87% of the adequate intake (Masullo *et al.* 2015). Inadequate intake of certain vitamins and minerals by those following the Swank and Paleo diet suggests that these diets may be too restrictive, thus further research is needed. A revival of interest among MS researchers for the therapeutic potential of the CAM therapies (diet, omega-3 fatty acids and antioxidants was reported (Yadav *et al.* 2010b). The effect of PUFA supplementation in MS has been extensively investigated, but with equivocal outcome. Recently, meta-analyses of epidemiological studies (Farinotti *et al.* 2012; Kong-Gonzalez *et al.* 2015) evaluated the benefits of dietary supplementation with PUFAs, especially omega-3 fatty acids, in relation to inflammatory, autoimmune and neurodegenerative disorders. The results (based on insufficient data and design limitations) were ambiguous, suggesting some evidence of a protective effect of PUFAs in MS, with a tendency to reduce the frequency of relapses, however without a major effect on MS progression.

The evaluation of three double-blind trials with LA (18:2, n-6) in early MS showed reduction of increase in disability, severity and duration of relapses (Dworkin *et al.* 1984). Fish oil supplemented together with vitamins and dietary counseling improved the clinical outcome in newly diagnosed MS patients (Nordvik *et al.* 2000). On the other hand, a clinical trial with n-3 PUFA treatment in acute relapsing MS showed no significant differences (Bates *et al.* 1989). However, there was a favorable trend of the n-3 PUFAs-treated group on parameters like overall deterioration, as well as the frequency, severity and duration of relapses. The discrepancies between these studies may be explained by different criteria for patient selection (clinical subtype of MS), and different disability scores at the start of the study (Gallai *et al.* 1992).

The nutritional studies were focused on the administration of dietary supplements (Farinotti *et al.* 2012) or on the assignment of diets low in saturated fat, either without supplements (Swank and Goodwin 2003a) or combined with omega-3 fatty acids supplements (Nordvik *et al.* 2000; Weinstock-Guttman *et al.* 2005). Other clinical trials were based only on the administration of single dietary supplements such as vitamin D (several, mostly ongoing studies), fish oil (n-3 PUFAs; (Ramirez-Ramirez *et al.* 2013; Shinto *et al.* 2009) or lipoic acid (Yadav *et al.* 2010a). In a study evaluating the combined effect of a calorie-restricted, semi-

vegetarian diet and administration of vitamin D and other dietary supplements (fish oil, lipoic acid, omega-3 PUFAs, resveratrol and multivitamin complex) in MS patients with for 6 months, the investigators (Riccio *et al.* 2016) found no significant changes in neurological signs. However, serum levels of the activated isoforms of gelatinase matrix metalloproteinase-9 (a marker of the inflammatory status of the patient) decreased by more than 50% in MS patients.

Dietary supplementation of patients with relapsing remitting MS with hemp seed oil (~55% linoleic acid (18:2, n-6), ~20% α-linolenic acid (18:3, n-3)) and evening primrose oil (~75% linoleic acid (18:2, n-6), ~10% γ-linolenic acid (18:3, n-6)) for 6 months achieved significant improvement in EDSS (Rezapour-Firouzi *et al.* 2015).

Another study (Bates *et al.* 1989) reported a trend in improvement of disease severity measured by EDSS in a group of MS patients supplemented with EPA and DHA (from fish oil) when compared to the placebo group receiving oleic acid (from olive oil). The results did not achieve statistical significance favoring omega-3 fatty acids supplementation, probably due to the not so optimal study design, because both study groups were advised to follow a diet low in animal fat and high in omega-6 PUFAs. Importantly, both groups developed changes in serum fatty acids levels over the 2 years of the study, which may indicate a diet effect in the placebo group as well.

A similar study with EPA and DHA supplementation together with a diet low in animal fat and high in n-6 PUFAs was conducted in MS patients and matched healthy controls (Gallai *et al.* 1995). A significant decrease of the proinflammatory cytokines (IL-1β, TNF-α and IL-2) as well as proinflammatory eikosanoids (prostaglandin E2 and leukotriene B4) secreted from peripheral blood mononuclear cells of MS subjects and healthy controls was observed after 6-months of supplementation, supporting the suggestion of immunomodulatory effect of n-3 PUFA supplementation.

Recent analysis (Riemann-Lorenz *et al.* 2016) revealed that patients with MS significantly more often adhered to a ”Mediterranean Diet“ than controls. More than 1/3 of the MS patients had tried special MS diets.

It is known that sunnier, lower-latitude region has lower MS prevalence, than high-latitude region with less solar radiation. Vitamin D, which produced by the action of ultraviolet B rays in the skin, has beyond its role in calcium homeostasis and bone health, immunomodulatory effects and reduces markers of oxidative stress (Dankers *et al*. 2017; Pierrot-Deseilligny and Souberbielle 2017). Majority of MS patients has vitamin D deficiency, showing seasonal

variation. There is an inverse association of serum levels of vitamin D and the seasonal risk of MS relapse (Hartl *et al.* 2017). Although studies in experimental autoimmune models strongly suggest the protective role of vitamin D in human autoimmune diseases (Dankers *et al*. 2017), the results of vitamin D supplementation in MS patients were rather inconsistent. There were both positive (Burton *et al.* 2010; Soilu-Hänninen *et al.* 2012) and no-effect (Kampman *et al*. 2012; James *et al*. 2013) results for disease outcomes, such as EDSS, MRI lesions, functionality, and relapse rates. Safety data suggests that high dose vitamin D is well tolerated and associated with minimal risk.

A low animal fat diet, omega-3 PUFA, lipoic acid and vitamin D supplementation as potential anti-inflammatory and neuroprotective agents in both relapsing and progressive form of MS are probably the most promising CAM therapies that warrant further investigation. The positive effects for the MS patient consist in less deterioration, lower relapse rate and reduced severity and duration of relapses.

High fiber diets, gut microbiota and CNS function

High fiber diets have numerous reported health benefits in reducing risk of obesity, type 2 diabetes, colon cancer, stroke, and cardiovascular diseases, making it a widely recommended healthy diet. CNS and gut are connected through enteric nervous system, autonomic nervous system, immune system, or the metabolic processes of gut microorganisms (microbiota). Many of the reported diet-linked beneficial effects have been associated with the microbiome and its ability to produce short-chain fatty acids (SCFA), like butyrate. Part of the short-chain fatty acids, produced during the colonic fermentation can be absorbed, taken up by the liver and utilized by various tissues (Tarini and Wolever 2010; Wolever and Chiasson 2000). There are many reports of high fiber diets increasing blood levels of circulating butyrate (Priebe *et al.* 2010; Robertson *et al.* 2005; Wolever and Chiasson 2000). Some researchers hypothesized the possibility that circulating butyrate could affect CNS function directly. A recent study demonstrated that germ free mice have increased BBB permeability, when compared with specific pathogen free mice containing a healthy microbiota (Braniste *et al.* 2014). After colonization of the germ free mice with the butyrate-producing bacteria, Clostridium tyrobutyricum, or an oral gavage (for 3 days) of sodium butyrate, BBB permeability restored to the levels of the pathogen free mice. This study demonstrated the strong and important connection between the microbiota, butyrate and the brain. Another study found that mice fed with the soluble fiber diet showed an increase in interleukin 1 receptors A, a cytokine and inhibitor of the pro-inflammatory IL-1β, in the brain after exposure to the lipopolysaccharide

and a decrease in IL-1β and TNF alpha (Sherry *et al.* 2010). Thus, the authors hypothesized that the elevated butyrate from the dietary fiber fermentation may contribute to the immune response. In contrast to the soluble fiber diets, splenocytes from mice on the insoluble fiber diet did not increase IL-4 production when exposed to butyrate *in vitro*.

Butyrate is a multi-functional molecule that has significant potential as a therapeutic for the brain, both in its pharmacological and dietary form. The source of butyrate in a high fiber diet or in a diet rich in natural butyrate is a highly appealing approach, as it presents a simple and relatively low risk method to potentially improve outcomes in patients with brain disorders. However, much more research is needed to understand the effectiveness of these dietary interventions.

Recently, a paper was published about cooperation of commensal microbiota and myelin autoantigen to trigger autoimmune demyelination (Berer *et al.* 2011). The gut microbiota is composed of trillions of microbes that perform several tasks essential to our physiology. Recent emerging evidences have suggested the important contribution of gut microbiota in several biological functions of mammals, such as the regulation of the immune system, metabolism, intestinal development or brain physiology (Al-Asmakh *et al.* 2012; Carabotti *et al.* 2015; Mayer *et al.* 2015; Petra *et al.* 2015; Tillisch 2014; Umbrello and Esposito 2016). In fact, recent works, mainly performed in experimental model of MS, have demonstrated that resident commensal microbiota can modulate CNS autoimmunity (Berer *et al.* 2011; Lee *et al.* 2011; Ochoa-Reparaz *et al.* 2009; Yokote *et al.* 2008). The microbiota is now known to shift the balance between protective and pathogenic immune responses in the CNS and in other organs as well. As regards to CNS physiology, the gut microbiota influences synaptogenesis, regulates neurotransmitters and neurotrophic factors release and function (Diaz Heijtz *et al.* 2011). A recent study (Miyake *et al.* 2015) revealed that MS patients have a microbial imbalance (dysbiosis) in their gut microbiota that is most likely linked to the disease pathogenesis. There is growing evidence that gut microbes produce neurotransmitters, such as GABA and serotonin, modulate the immune system, alter epigenetic markers and produce bioactive food components and energy metabolites (Berer *et al.* 2011; Diaz Heijtz *et al.* 2011; Hooper 2004). Thus, dietary manipulation to achieve a symbiosis that can improve the health of the microbiome and our brains is an attractive idea currently under investigation. Butyrate, the SAFA produced by colon bacteria, has a role as a potential therapeutics for neurological diseases. The dietary sources of butyrate, either a high fiber diet or a diet rich in natural sources of butyrate, is a highly appealing approach, as it presents a simple and relatively low risk method to potentially improve outcomes in patients with brain disorders.

Pharmacologically, butyrate has had a profound beneficial effect on brain disorders ranging from neurodegenerative diseases to psychological disorders. (Bourassa *et al.* 2016). However more research is needed to understand the effectiveness of these dietary interventions.

Conclusions

Dietary intervention is a highly appealing approachto potentially improve outcomes in patients with brain disorders. However much more research is needed to be confirmed in the long term and well defined studies to understand the effectiveness of these dietary interventions.

Dietary advices represent a simple and relatively low risk methods to improve the outcomes in patients with MS, mainly to reduce severity and duration of relapses, to lower relapse rate, to reduce the rate of progression and to decrease the deterioration of the patient. To lower the dietary intake of saturated animal fat is recommended generally, not only for patients with MS. According to the reviewed studies, diet with increased intake of PUFAs, of n-6 group (vegetables, seeds oils), but mainly of n-3 group (EPA and DHA from fish oil), food rich in fiber, supplementation with lipoic acid and vitamin D could have beneficial effect in MS patient.

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