DOI: 10.1590/0004-282X20140159

Modifiable environmental factors in multiple sclerosis

Fatores ambientais modificáveis na esclerose múltipla

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ABSTRACT

Potential environmental modifiable factors involved in multiple sclerosis (MS) include low adherence to treatment, smoking, obesity, low levels of liposoluble vitamins A and D, high consumption of salt, and a sedentary lifestyle. Chronic tobacco use, obesity, sedentarism and insufficient levels of these vitamins all contribute to maintenance of a proinflammatory state. It is unlikely that there will be noticeable improvement in the inflammatory condition of MS if stopping smoking, reducing weight, exercising, increasing vitamin levels are done in an isolated and erratic manner. Modification of each and every one of these environmental risk factors is likely to be an important approach in the management of MS. The present review presents the arguments for an association between these hazardous modifiable factors and the chronic inflammatory state observed in MS.

Keywords: multiple sclerosis, smoking, obesity, vitamin D, vitamin A, exercise.

RESUMO

Potenciais fatores ambientais modificáveis envolvidos na esclerose múltipla (EM) incluem baixa adesão ao tratamento, tabagismo, obesidade, baixos níveis das vitaminas lipossolúveis A e D, e um estilo de vida sedentário. O uso crônico de tabaco, obesidade, sedentarismo e níveis insuficientes destas vitaminas podem todos contribuir para a manutenção de um estado pró-inflamatório. É pouco provável que haja melhora notável na condição inflamatória da EM se a cessação do tabagismo, a redução de peso, exercícios e maiores níveis de vitaminas forem obtidos isoladamente e de maneira errática. A modificação de cada um destes fatores de risco ambientais poderá ser importante parte do manejo eficaz da EM. A presente revisão apresenta argumentos para uma associação entre os fatores modificáveis nocivos e o estado inflamatório crônico observado na EM.

Palavras-chave: esclerose múltipla, tabagismo, obesidade, vitamina D, vitamina A, exercícios.

Evidence for the inflammatory pathogenic basis of multiple sclerosis (MS) is overwhelming. This chronic neurological disease is characterized by demyelination, multifocal inflammation, reactive gliosis and axonal/neuron loss[1].

The most effective treatments for MS are immunosuppressive in nature and may, for example, include monoclonal antibodies such as natalizumab [NTZ], daclizumab [DCL], and alemtuzumab [ATZ]. Patients with MS who do not respond to immunomodulatory drugs (first-line therapy) receive immunosuppressive drugs (second-line therapy), which have the risk of potentially fatal adverse events. The monoclonal antibodies recommended for MS treatment may have to be withdrawn after a certain period of use, due to intolerance of side effects. At this time, MS may reactivate with severe inflammatory reactions[2].

It is possible that, with a specific approach to modifiable factors, the use of more aggressive treatment may not be necessary and the patient might thrive on immunomodulatory drugs that have less severe side effects. However, when the patient presents an aggressive form of MS and/or does not respond to immunomodulatory drugs[3], the immediate reaction is to progress to immunosuppression[4].

Perhaps it is time to consider the modifiable factors in MS when treating a patient. It goes without saying that adequate adherence to treatment needs to have been confirmed before the patient is given second-line therapy with potentially more serious, and even fatal, side effects. Through quitting smoking, losing weight, exercising and maintaining proper serum levels of vitamins A and D, the patient may respond better to all pharmacological treatments. It is, after all, the environmental factors that perpetuate the inflammatory state in MS and, for unknown reasons, these factors are frequently ignored. A summary of the potentially modifiable factors in presented in Table.

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Conflict of interest: There is no conflict of interest to declare.

Received 18 June 2014; Received in final form 16 August 2014; Accepted 04 September 2014.

Table. Summary of the effects of modifiable environmental factors in multiple sclerosis (MS). Simple changes in lifestyle are capable of altering the pro-inflammatory state of MS, inducing favorable shifts towards homeostasis and an anti-inflammatory state.

Smoking obesity	Induces apoptosis, leads to the release of both inflammatory cytokines and matrix metalloproteinases Promotes of inflammation due to an anergic state of Treg cells
Vitamin A	Promotes homeostasis between Th1, Th2, Th17, Tregs, B cells and dendritic cells
Vitamin D	Suppresses TNFα, IL-12 and inducible NO synthase, induces Th2 cells and IL-10 expression
Exercise	Reduces plasma levels of interferon gamma and IL-17
Low salt diet, omega-3 and probiotics	Reduces induction of Th17 lymphocytes

SMOKING

Cigarette smoking increases the risk of developing autoimmune diseases and leads to worse disease evolution for patients suffering from immunological diseases[5]. The relative risk of developing MS among smokers is almost twice that of never-smokers[5,6]. Cigarette smoke is capable of increasing the expression of Fas on B and CD4 T lymphocyte cell surfaces[7]. Fas (CD95) is a pro-apoptotic transmembrane protein that also induces release of inflammatory cytokines by macrophages[8]. In addition, cigarette smoking leads to release of matrix metalloproteinases[9] and affects immunological homeostasis[10,11].

Patients with MS who smoke have a more severe disease course and a faster disability progression rate[12,13]. Furthermore, smokers run a risk of developing antibodies against natalizumab that is almost three times higher than that of non-smokers[14]. A recent meta-analysis has shown that, independently of the type of study, smoking is associated to MS[15]. An interesting and recent study points out that smoking is associated to MS only for certain genotypes, characterizing a situation where environmental and genetic factors interact[16].

Passive smoking also increases the risk of developing MS[17] and it is advisable that patients with MS should not be exposed to environments with tobacco smoke.

OBESITY

Individuals who were overweight or obese during childhood or adolescence have twice the risk of developing MS in adulthood[18,19,20]. In fact, other autoimmune diseases are also more common in individuals who are above the proper weight[21]. Exposure to the so-called "Western diet", which includes high fat and cholesterol, high protein, high sugar, and excess salt intake, promotes obesity, metabolic syndrome, cardiovascular disease and autoimmune diseases[22].

White adipose tissue is not an inert tissue devoted solely to energy storage. Adipocytes can be regarded as part of an endocrine organ that releases several proinflammatory mediators, such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), leptin and C-reactive protein[23]. A small number of adipocytes have anti-inflammatory properties and release the beneficial protein adiponectin[24]. In the presence of obesity, production and/or secretion of these factors may be dysfunctional, leading to obesity-related disorders, including autoimmune diseases.

One key player in the immunological tolerance response that can be affected by obesity is regulatory T cells (Tregs). These are forkhead box P3 (FOXP3)$^+$ T cells that have pivotal importance in the mechanisms controlling immunological homeostasis and function[25]. Leptin, one of the inflammatory cytokines released by adipocytes, can affect the function of Tregs[26]. Administration of an anti-leptin antibody has been found to succeed in reversing the anergic status of Tregs *in vitro*, enabling them to proliferate in response to anti-CD3 and anti-CD28 stimulation[27]. *In vivo*, a significant inverse correlation is observed between the number of Foxp3 Treg cells and body weight and plasma leptin levels[28]. Leptin has also been found to promote Th17 inflammatory responses in normal human CD4(+) T cells and in mice, both *in vitro* and *in vivo*[29,30]. Leptin is also a major contributor to vascular damage in obesity-related cardiovascular diseases, which are not the subject of the present review[31]. However, it is clear that cardio and cerebrovascular complications in a patient with MS represent an extra burden on the patient, the family and society.

VITAMIN A

Retinoic acid (RA), the active metabolite of vitamin A, modulates the functional balance between Th1, Th2, Th17, Tregs, B cells and dendritic cells[32]. RA plays a major role both in increasing tolerance and in decreasing inflammation, and RA synthesis may be manipulated by the complex cross-talk among cells during infection and inflammation[33].

Specific receptors for RA, namely RXRγ, can promote remyelination by acting on oligodendrocytic precursor cells[34]. It has long been known that RA suppresses development of autoimmune experimental encephalitis (EAE) in rats[35] in association with increased IL-4 levels in the animal[34].

Although studies on vitamin A supplementation are at a nascent stage, it is reasonable to maintain normal retinol values in the plasma of patients with MS. Intake of foods that are rich in carotenoids and retinyl esters, which are both precursors of retinol, must be encouraged. Serum

levels of retinol should be assessed in the same manner in which vitamin D metabolites are now regularly assessed in patients with MS. It is important to highlight that no supplementation with vitamin A has ever been tested or proven effective for the treatment of MS and excess vitamin A can be fatal.

VITAMIN D

Over the last decades, studies on vitamin D, immune-mediated diseases, cancer and bone metabolism have shown that homeostasis of vitamin D is crucial.

Vitamin D is almost immediately hydrolyzed in the liver by 25-hydroxylase to 25-hydroxyvitamin D (25(OH)D). This circulating metabolite of vitamin D best reflects the vitamin D status of the patient, but 25(OH)D can be further hydrolyzed to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) or calcitriol. This is the biologically active metabolite of vitamin D[36].

Vitamin D is a hormone with important immunological roles. IL-10 expression is induced by $1,25(OH)_2D$ in different cells of the immune system. Vitamin D has a direct effect on naive CD4(+) T cells, leading to development of Th2 cells[37]. Macrophages conditioned with $1,25(OH)_2D_3$ potently suppressed the expression of pro-inflammatory parameters such as TNFα, IL-12 and inducible NO synthase (iNOS)[38,39].

Low serum levels of 25-hydroxyvitamin D (25[OH]-D) were found to correlate with MS activation and progression over five years in a large population of individuals presenting a first demyelinating episode[40]. This finding was independent of treatment with interferon beta. Vitamin D3 add-on treatment to interferon beta reduced the activity of MS in relation to patients treated only with interferon beta, as assessed by magnetic resonance imaging[40,41]. On the other hand, there are also very sound studies showing that vitamin D has a disputable relation to MS[42,43].

Even if an association between MS and vitamin D is considered to exist, the correct manner in which to proceed with supplementation, if necessary, remains a matter to be clarified in the future[44]. However, it is advisable that patients with MS should maintain normal serum levels of vitamin D, and be encouraged to eat foods that are sources of this vitamin. Moderate sun exposure at early hours of the day is also essential if vitamin D levels are to be corrected.

It is important to observe that $1,25(OH)_2D$ and RA have synergistic effects on the regulation of T cells, in particular Th17[45]. To give supplements of one vitamin and not the other may negatively influence their effects on Th17 cell-related immune diseases[32,33]. It is, therefore, likely that vitamin D supplementation will be less effective in patients with MS whose levels of vitamin A are insufficient. In fact, dietary intake of all vitamins should be encouraged rather than supplementation with pills.

It is also of importance to emphasize that high doses of vitamin D are hazardous and should not be used, especially because there is no scientific evidence of its efficacy.

EXERCISE

Exercise in MS is more than rehabilitation. It is a form of treatment that does not lead to adverse events and can be quite inexpensive. Several types of exercises have been studied, and aerobic training, endurance exercises, exercise classes, aquatic exercises and yoga have all been shown to be beneficial in relation to several aspects of the disease, including fatigue, depression and disability[46]. Exercise induces favorable changes in T cells by reducing plasma levels of interferon gamma and IL-17[47]. Secondary benefits from regular physical activities include somatic-affective improvement in mood[48]. In fact, exercise and physical activity may have beneficial effects on depression symptoms that are comparable to those of antidepressant treatments[49].

LOW SALT DIET, OMEGA-3 AND PROBIOTICS

High salt (sodium chloride) diet has been shown to boost the induction of Th17 lymphocytes both in animal models and in humans[50,51]. The Th17 cells generated under high-salt diet appear to be highly pathogenic and related to pro-inflammatory cytokines. Although still an experimental observation that needs epidemiological confirmation, it is important to alert the patients about this potentially hazardous factor.

A diet rich in omega-3 unsaturated fatty acids, polyphenols and probiotics has been described to influence the development and character of regulatory T lymphocytes, or T regs[52,53].

ALCOHOL

A dose-dependent association between alcohol consumption and the risk of developing MS has been shown recently[54]. Patients with MS seem to have a tendency to misuse alcohol, but only very few studies have been carried out on the subject[55]. At least *in vitro*, ethanol can induce a cytokine profile consistent with a Th17 regulatory phenotype[56]. A further complication of the long-term alcohol consumption in patients is, obviously, the cognitive alterations induce both by ethanol and MS.

DISCUSSION

The pathogenic inflammatory aspects of MS are of major importance regarding treatment. The presently approved

treatments are all anti-inflammatory and have variable efficacy, which generally speaking, is positively associated with the severity of side effects. To declare that a patient is not responsive to a particular treatment implies that all possible ways of controlling the inflammation have been taken into consideration. Modifiable factors could be specifically discussed with the patient during routine consultations. Although most patients seem to be willing to receive high doses of vitamin D (even megadoses, without any scientific evidence for their use), not too many patients seem to be willing to stop smoking, drinking, starting with exercise and weight loss programs. In fact, there are reports clearly showing that patients are willing to run the risk of life-endangering side effects from immunosuppressive drugs for MS in order to continue with the treatment[57,58]. Furthermore, thousands of patients with MS worldwide were found to be willing to submit themselves to a vascular surgical procedure to treat their MS for which there was no scientific basis[59]. The evidence arising from these events therefore begs the following questions: Should modifiable factors be so difficult to modify, given that the methods are inexpensive and safe? Are we doing enough to resist the introduction of immunosuppressive treatment for patients with MS?

Introduction of a diet rich in vitamins A and D can contribute towards weight loss. Exercise will be beneficial both for the disease and for weight management. With a healthier lifestyle, better nutrient intake and regular exercise, the patient is likely to be less resistant to stopping smoking and drinking. It is perhaps time to consider more than just supplementation of vitamin D for patients with MS[60,61]. In fact, single supplementation of vitamin D (often at high doses or even megadoses) may alter the delicate immunological homeostasis that occurs between vitamin D and vitamin A[33]. Other life style habits, such as chronic caffeine ingestion, may also be related to the development of MS and further research into other modifiable factors is urgently needed. The criteria for therapeutic failure of a treatment are clearly related to inflammation and its lack of control, e.g., relapses and lesions in the brain and spinal cord[62]. Thus, if a patient does not respond well to a given treatment, perhaps we should ask ourselves whether everything that could be done to decrease inflammation has indeed been done. At the same time, in our daily practice, we should encourage all patients to modify the factors that prolong their exposure to inflammatory cytokines since the very beginning of the disease. In time, perhaps we will see that our future rate of non-responders may not the same we have now.

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