

REVIEW

The Multiple Factors of Multiple Sclerosis: A Darwinian Perspective

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Abstract

Purpose: Multiple sclerosis (MS), an autoimmune disease of the central nervous system, is often referred to as a multifactorial disease, but there is little consensus as to what factors are involved, besides genetic susceptibility and childhood infectious agents. The purpose of this paper is to identify plausible, environmental factors that contribute to the aetiology of MS.

Design: Review of the published literature.

Materials and Methods: The probable environmental factors that promote MS onset and progression have been deduced from principles of evolutionary biology in conjunction with the currently accepted disease process. All environmental factors that either promote the activation of self-reactive immune cells or decrease immune regulation are considered to be potential causal factors. Those potential factors for which there are diverse inductive data that link them to MS onset and progression are deemed to be plausible, causal factors.

Results: This analysis identified seven likely causal factors, all of which have been introduced into the human environment in the past 10,000 years by the agricultural, industrial and technological revolutions. Factors that promote the activation of autoreactive immune cells: (1) infectious agents that have crossed over from domesticated animals; (2) new food types introduced by agriculture (dairy, grains, legumes); (3) reduced fibre consumption in concert with an excessive intake of sugar, starch and antibiotics. Factors that decrease immune regulation: (4) deficiency in vitamin D; (5) deficiency in omega 3 essential fatty acid (EFA) in concert with an excess of omega 6 EFA; (6) deficiency in antioxidants in concert with increased oxidative factors; (7) paucity of chronic infections due to the establishment of hygienic conditions.

Conclusions: The greatly increased supply of cross-reactive antigens from agriculture, in combination with decreased immune regulation from industrialization, has resulted in a huge increase in the incidence and prevalence of MS over the past 200 years. The identification of these probable causal factors of MS leads to common sense, nutritional strategies for reducing the risk of MS and for helping those with MS control disease progression.

Keywords: multiple sclerosis, environmental factors, vitamin D, infectious agents, evolutionary biology, nutritional strategies.

INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) and results in a myriad of disabilities that increase over time [1]. It is interpreted

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that a number of environmental factors act in concert with genetic susceptibility to cause MS, but there is no consensus as to the specific factors that cause MS [2]. Given that a determination of the probable causal factors of MS would potentially lead to the development of one or more effective therapies for both treating and reducing the risk of MS, it is important to attempt to identify these factors. Here, such an attempt has been made by using a combination of deductive reasoning and an appraisal of the inductive database for MS.

The deductive approach relies on the currently accepted model for MS pathogenesis and on principles of evolutionary biology. It is reasonable to assume that the genes that result in MS susceptibility would not be favoured by natural selection. Thus, such susceptibility genes must have once positively contributed to human fitness but, due to one or more recent environmental changes, they now have a negative effect. In evolutionary terms, MS can be seen as an agent of elimination of such genes that are no longer compatible with our present environment (negative selection). Instead of asking what environmental factors cause MS, a Darwinian (evolutionary) perspective first asks what environmental changes have occurred to adversely affect the human genome such that formerly beneficial genes now drive various pathogenic reactions that result in the MS disease process.

THE DISEASE PROCESS OF MS

MS is currently interpreted to be a cell-mediated, autoimmune disease [3]. However, there may well be two different disease types that are now bundled together under MS. Lucchinetti *et al.* [4] found that, although the majority of cases of MS had indicators of an autoimmune pathogenesis, some were characterized by the death of myelin-producing cells (oligodendrocytes) due to either a toxin or viral infection. Here, the plausible causal factors of autoimmune MS, which is the classic disease type, will be discussed.

Autoimmune disease involves both the activation of immune cells that are sensitized to one or more self-antigens and the failure of the regulatory side of the immune system to control such pathogenic reactions. In MS, self-antigens associated with myelin are attacked by the immune system. Myelin is the substance that wraps around and insulates the nerve axons of the CNS and the loss of myelin due to inflammatory reactions can lead to the destruction and degeneration of the axons themselves. The loss of myelin and axons due to ongoing inflammation and degeneration results in the various disabilities that characterize MS [5].

The currently accepted model for the MS disease process involves the activation of myelin-sensitive, T helper 1 cells in the periphery by interactions of the immune system with foreign proteins [6]. The activated T cells migrate to the brain, cross the blood–brain barrier and initiate a complex immune response against one or more self-antigens associated with proteins in myelin. These inflammatory reactions are poorly controlled and result in substantial damage to tissue in the CNS.

This model begs the question of how foreign proteins activate autoreactive T cells that are sensitized to one or more myelin antigens. The favoured answer to this question is that such self-reactive T cells become activated through molecular mimicry [6, 7]. Molecular mimicry occurs when a fragment of a foreign protein that is presented to the immune system in the context of a specific major histocompatibility complex (MHC) molecule closely resembles a self-antigen. Thus, a T cell that becomes activated against the foreign antigen also has the capability of attacking the look-alike, self-antigen that, in the case of MS, resides in a myelin protein. Such immune reactions are known as cross-reactions. There are other, less favoured, proposed mechanisms for the activation of autoreactive T cells by foreign proteins [8].

FOREIGN PROTEINS AND MS

It can be reasonably assumed that genes that promoted autoimmune reactions with common foreign proteins would have been gradually eliminated from the gene pool over 4 million years of human evolution (natural selection). The current widespread occurrence of a variety of autoimmune diseases, especially in first world populations, indicates that new foreign proteins, for which the human genome has little evolutionary experience, are now in the human environment. Abundant new foreign proteins were introduced by the agricultural revolution that occurred between 10,000 and 5000 years ago [9]. The new proteins came from infectious agents that crossed over to humans from domesticated animals and new, protein-rich, food types. Examples of new infectious agents include the herpes family of viruses and influenza viruses, as well as many bacteria. The new food types introduced by agriculture include dairy products, grains and legumes [10]. These new foreign protein sources contain innumerable novel antigens. The lack of evolutionary experience with these new antigens would have ensured that many of them would have had the potential to cause cross-reactions with self-antigens.

For the infectious agents, there is a great deal of inductive data linking them to MS [11]. Such data include epidemiology, animal experiments and immunology [12]. Numerous studies have shown that Epstein–Barr virus (EBV) and other viruses and bacteria yield antigens that cause cross-reactions with self-antigens associated with myelin [13]. The current database leaves little doubt that a variety of these infectious agents are probably part of the activation of myelin-reactive immune cells [14].

In regard to food proteins and autoimmune disease, the only undisputed causal factor of a cell-mediated autoimmune disease is an antigen derived from gluten grains (celiac disease) [15]. There are abundant data from studies in epidemiology, animal experiments, immunology and small clinical trials that implicate antigens derived from proteins associated with the foods introduced by agriculture in MS and other cell-mediated autoimmune diseases. Various proteins from cows' milk, grains and legumes have been shown to yield molecular mimics of self-antigens in the CNS, joints, eyes and pancreas [16–19].

A number of studies have demonstrated that antigens from milk proteins can initiate cross-reactions with self-antigens associated with myelin [16, 20, 21]. These milk-derived antigens can also cause experimental autoimmune encephalomyelitis (EAE), an MS-like disease, in laboratory animals [20]. One study found that T cells reactive with dairy antigens were common in persons with MS, but very rare in healthy controls [16]. Another important linkage between dairy and MS is the close correlation between the amount of dairy consumed and MS prevalence [22].

Experimental type 1 diabetes, rheumatoid arthritis and uveitis have been induced in genetically susceptible mice and rats by feeding them dairy products, grains or legumes [18, 20, 23, 24]. Small clinical trials in rheumatoid arthritis and Crohn's disease have demonstrated that the avoidance of these food types has resulted in substantial improvement of disease symptoms [25, 26].

MS AND INCREASED INTESTINAL PERMEABILITY

Because infectious agents invoke a substantial immune response and can readily come into contact with the immune system in the lungs and intestinal tract, it is not difficult to accept the interpretation that infectious agents are involved in MS. Food proteins usually do not invoke an immune response because of restricted passage across the intestinal barrier that separates intestinal contents from the circulatory system. Furthermore, the phenomenon of oral tolerance usually results in the lack of an immune response when antigens derived from food proteins meet the immune system [27].

One way that fragments of food proteins cross the intestinal barrier before being broken

down into amino acids is through a damaged intestinal wall ('leaky gut'). Increased intestinal permeability can be due to various factors, including gastrointestinal infections, bacterial or fungal overgrowths, stress, pharmaceuticals, food allergies and lectins [28, 29]. If potentially immunogenic food proteins pass through the intestinal barrier in the presence of an infectious agent, food antigens can be seen as 'dangerous' and can invoke an immune response [18]. Memory cells sensitive to antigens from food proteins would be established and such immune cells would be activated each time they encountered the food-derived antigens. If the food antigen was a molecular mimic of either a myelin antigen or an infectious antigen that cross-reacted with a myelin antigen, such food antigens could activate myelin-sensitive memory T cells. Such three-way molecular mimicry between food antigens, infectious antigens and self-antigens has been demonstrated for rheumatoid arthritis [17] and experimental uveitis [18].

Thus, causal factors in MS include environmental factors that adversely affect the integrity of the intestinal barrier.

- (1) Infectious agents that crossed over from domesticated animals. These can cause inflammation of the gut wall and increased permeability.
- (2) New food proteins that can cause allergenic reactions and yield lectins. The recent practice of feeding such food proteins to babies less than 1 year old further increases the chance of problematic immune responses to these foods [30].
- (3) A deficiency in fibre due to a great decrease in the consumption of vegetables and fruits and a corresponding increase in the consumption of grains and sugar. These factors, as well as antibiotics, adversely affect the gut flora and these floral changes can cause increased gut permeability and altered immune function [31, 32].

Studies that support this concept include one that found that five out of 12 MS patients had abnormal jejunal mucosa [33] and one that found that five out of 20 MS patients had increased intestinal permeability [34]. A recent study demonstrated that persons with MS have 'moderately increased uptake of some specific proteins from the gut in MS', the signature of increased intestinal permeability [35].

MS AND REDUCED IMMUNE REGULATION

Factors that adversely affect the suppression of autoimmune reactions are also important in MS pathogenesis [36]. Such factors can be deduced by examining recent environmental changes that can theoretically decrease the capacity of the immune system to suppress autoimmune reactions.

In pre-agricultural times, the human diet consisted mainly of vegetables, fruits and low-fat, wild animals [10]. Other important environmental conditions included a high supply of vitamin D from frequent exposure to subtropical ultraviolet radiation [37] and common, low-grade, chronic infections due to unhygienic conditions [38]. The adoption of agriculture has substantially changed the human diet such that high-fat, grain-fed domesticated animals are the main meat supply and sugar and grains, rather than fruits and vegetables, are the main carbohydrates consumed [10].

Humans have gone from a relatively low-fat diet with a balance of fat types, including substantial omega 3 essential fatty acid (EFA), to a high-fat diet dominated by saturated fat and omega 6 EFA (margarine, vegetable oil) and a near absence of omega 3 EFA [39]. This has decreased immune regulation because omega 3 EFA is the main fat type that results in immune suppression [40]. The great decrease in fruits and vegetables has resulted in a reduced intake of antioxidants and this has also decreased immune regulation.

There has been a huge decrease in vitamin D supply due to migration to higher latitudes and major shifts in lifestyles (clothes, homes, offices, sunscreen) [37, 41]. Once again, this great decrease in vitamin D negatively affects immune suppression. Finally, the elimination

of chronic infections (e.g. parasites) due to ultra-hygienic conditions leads to an undereducated immune system with a reduced capacity for immune suppression (hygiene hypothesis) [38].

There is much inductive science that supports the involvement of these new environmental conditions in MS. The greatest amount of evidence deals with the linkage between MS and the reduced supply of vitamin D [42–44].

- (1) Epidemiological data from Australia showed an excellent correlation between vitamin D supply through ultraviolet radiation and MS prevalence [45]. Notably, the correlation between ultraviolet radiation and MS was stronger than that for ultraviolet radiation and melanoma [45].
- (2) Increased sun exposure as a child significantly reduced MS risk in Tasmania [46].
- (3) Nurses who used a vitamin D supplement had a 40% reduction in MS risk [47].
- (4) Immunological studies demonstrated that the active hormone metabolite of vitamin D suppressed inflammatory immune reactions [48].
- (5) Injections of the active vitamin D hormone prevented and halted EAE in laboratory animals [49, 50].

Omega 3 EFA has been shown to be of benefit in animal experiments and small clinical trials for both rheumatoid arthritis and Crohn's disease [51, 52]. In regard to MS, a small clinical trial used fish oil as a therapeutic agent and 80% of individuals with probable MS were attack-free for the 2 year trial period [53]. In a recent controlled study of individuals with relapsing-remitting (R-R) MS, it was demonstrated that a low-fat diet with supplemental omega 3 EFA 'was associated with beneficial effects on QOL, clinical and immunological parameters' (Weinstock-Guttman, pers. comm.). The increased consumption of omega 6 EFA may also be a risk factor for MS by raising the omega 6/omega 3 ratio and preventing omega 3 EFA from contributing to immune regulation [54].

Oxidation is an important component of the inflammatory process and increased antioxidant activity appears to be anti-inflammatory [55, 56]. One study found that individuals with MS had significantly increased oxidative stress, especially during exacerbations [57]. The determination that smoking is a risk factor for MS also suggests that a decreased antioxidation capacity is a causal factor in MS [58]. Studies that support this are animal experiments that found that powerful antioxidants prevented EAE [59, 60]. Finally, it was recently demonstrated that flavonoids, antioxidants found in fruits, protect myelin from immune-mediated damage [61].

Bach [38] summarized the data and arguments that support the concept that the increased incidence of autoimmune and allergy diseases in first world populations is due in part to the establishment of hygienic conditions. The data indicate that the main reason for this phenomenon is the reduction in immune regulation capacity associated with the significant reduction in chronic infections [38, 62]. A dramatic manifestation of this concept is the very large increase in the incidence and prevalence of MS and type I diabetes (insulin-dependent diabetes mellitus) in Sardinia after World War II due to the eradication of malaria [63]. Further evidence comes from a study that showed that chronic infections prevented the occurrence of EAE in laboratory animals [64] and a recent investigation that demonstrated that children who live with younger siblings during the first 6 years of childhood are much less likely to develop MS [65]. Studies that have shown that higher social status is a risk factor for MS also provide support for the role of hygienic conditions in MS [66, 67].

ENVIRONMENTAL CAUSAL FACTORS OF MS

The above Darwinian deductions and accompanying inductive data indicate that the likely causal factors of MS are:

- (1) Infectious agents that have crossed over from domesticated animals.
- (2) New food types introduced by agriculture (dairy, grains, legumes).
- (3) Reduced fibre consumption in concert with an excessive intake of sugar, starch and antibiotics.
- (4) Deficiency in vitamin D.
- (5) Deficiency in omega 3 EFA in concert with an excess of omega 6 EFA.
- (6) Deficiency in antioxidants in concert with increased oxidative factors.
- (7) Paucity of chronic infections due to the establishment of hygienic conditions.

The first three factors contribute to increased activation of autoreactive immune cells and the last four factors contribute to a reduced capacity for immune regulation.

INFECTION/NUTRITION MODEL FOR MS AETIOLOGY

Taking into account the causal factors of MS, a model of MS aetiology can be formulated. In childhood, elements of the immune system in genetically susceptible persons are initially activated against myelin proteins by cross-reactions involving common infectious agents. If, at the time when these infections occur, immune regulation capacity is significantly reduced due to a low circulating vitamin D level, low omega 3 EFA intake, low antioxidant activity and/or an undereducated immune system, a significant pool of autoreactive memory T cells is established. An increased virulence of such infections (late onset) would help to establish the pool of autoreactive memory cells. Also, during childhood, immune sensitivity to various food proteins can develop due to increased intestinal permeability caused by various factors such as food allergies, a low fibre intake, antibiotics and gut infections.

Throughout childhood and early adulthood, autoreactive memory T cells are frequently reactivated through cross-reactions involving random infections and food antigens that episodically pass through a leaky gut. The pool of autoreactive memory cells continues to expand and diversify and the episodic activation of these cells, as well as naive autoreactive T cells, results in sporadic, subclinical, autoimmune attacks on myelin. Eventually, a cross-reactive event triggers a significant autoimmune attack on myelin that results in clinically apparent symptoms. MS is diagnosed as clinically apparent attacks continue to occur and CNS lesions are detected on a magnetic resonance imaging scan.

If any of these main events does not occur, then MS may never develop, despite genetic susceptibility and the presence of most of the other causal factors. This provides a reasonable explanation as to why monozygotic twins have a low concordance rate (25% and less) for MS [68]. The state of one's immune regulation capacity at the time of cross-reactive infections as well as the virulence of the infections are probably crucial factors in regard to whether or not MS will develop in later life.

THE RISE OF MS

MS appears to have occurred in only rare instances before the nineteenth century [2]. One reason for this is that, before that time, the vast majority of the population maintained adequate immune regulation through a reasonable vitamin D (outdoor activities) and omega 3 EFA supply (grass-fed animals and fish) and the occurrence of many more chronic infections due to unhygienic conditions. Thus, despite exposure to foreign proteins that had the potential to activate myelin-sensitive immune cells, the vast majority of genetically susceptible individuals were protected from MS.

MS began to become apparent during the nineteenth century [2] when lifestyle changes brought about by the industrial revolution resulted in substantially improved hygienic conditions and reduced vitamin D supply [69]. These changes lowered immune regulation capacity for many more people and made them more susceptible to MS.

During the twentieth century, environmental conditions continued to change such that immune regulation decreased for a larger portion of the population in the first world and MS became even more common. The main changes included:

- (1) A reduction in vitamin D due to more indoor jobs in urban environments, the use of sunscreen and the conscious avoidance of the sun due to the fear of skin cancer.
- (2) The increase in grain-fed animals and greater use of omega 6-rich vegetable oils, resulting in a much higher omega 6/omega 3 ratio [70].
- (3) The establishment of ultra-hygienic conditions throughout the first world.
- (4) A reduction in the consumption of fruits and vegetables and a consequent reduction in antioxidative capacity.

In summary, the loss of immune regulation capacity over the past 200 years, in combination with the already present, cross-reactive antigens, unleashed the MS monster in first world populations.

IMPLICATIONS FOR MS PREVENTION AND TREATMENT

The understanding that MS is caused by a variety of infectious and nutritional factors provides opportunities for devising and implementing various strategies to significantly lower the risk of MS for many people and to help control disease progression for those already diagnosed.

MS can probably be prevented in many cases by countering one or more of the causal factors in childhood. The simplest way to substantially reduce MS incidence is to ensure that children have an increased immune regulation capacity. This can be done by providing children with enough vitamin D to make sure their level of circulating vitamin D [25(OH)D] always remains above 80 nmol l^{-1} . This will require a 1000–4000 IU daily supplement for most [71]. An increased consumption of omega 3 EFA (2–3 g of docosahexaenoic acid (DHA)+eicosapentaenoic acid (EPA) per day) in concert with an increased intake of foods containing antioxidants will also contribute to increased immune regulation and decreased MS occurrence.

For those with MS, a decrease in autoimmune reactions can be accomplished by avoiding foods that contain proteins that can yield cross-reactive antigens (e.g. dairy products, grains and legumes). Strategies that prevent increased intestinal permeability would also be helpful. These include the avoidance of allergenic foods, an increased consumption of fibre, a decreased consumption of sugar and starch, the restricted use of antibiotics, and the use of probiotics [72].

An increased capacity for immune regulation can be accomplished with a few nutritional strategies, including:

- (1) Using an adequate vitamin D supplement to ensure that their level of circulating vitamin D always remains between 100 and 150 nmol l^{-1} . For most people this will require a daily supplement of 2000–4000 IU [71].
- (2) An increased consumption of omega 3 EFA through eating fatty fish and taking fish oil supplements. A daily intake of 3–5 g of DHA plus EPA is optimal [55]. A decreased consumption of omega 6 EFA and saturated fat will ensure that the omega 3 EFA will have a maximum effect.
- (3) An increased consumption of fruits and vegetables and the use of one or more antioxidant supplements. The discontinuation of smoking would be very helpful.

SUMMARY

The probable environmental causal factors for MS have been identified by making deductions based on principles of evolutionary biology in conjunction with the interpreted

disease process. Available inductive data provide additional support to these interpretations. The identified factors are:

- (1) Infectious agents that have crossed over from domesticated animals (e.g. EBV, HHV-6).
- (2) New food types introduced by agriculture (dairy, grains, legumes).
- (3) Decreased fibre consumption in concert with an excessive intake of sugar, starch and antibiotics.
- (4) Deficiency in vitamin D
- (5) Deficiency in omega 3 EFA in concert with an excess of omega 6 EFA.
- (6) Deficiency in antioxidants in concert with increased oxidative factors.
- (7) Paucity of chronic infections due to hygienic conditions.

All of these environmental factors are the result of the agricultural revolution and the industrial revolution. The agricultural revolution introduced many novel proteins for which humans had no evolutionary experience through the addition of new food types (dairy products, grains, legumes) to the human diet and by the crossover to humans of infectious agents from domesticated animals. These new proteins yielded innumerable novel antigens, with many having the potential to cause cross-reactions with self-antigens and thus promote autoimmune reactions. The introduction of these antigens did not cause widespread autoimmune diseases because most people had adequate immune regulation to suppress such reactions.

The industrial revolution introduced new environmental factors that substantially reduced immune regulation capacity for most of the population in high latitude countries. These new factors included vitamin D deficiency, omega 3 EFA deficiency, a reduction in antioxidant activity and a great reduction in chronic infections. The loss of the protective immune regulation capacity and the continuing presence of the cross-reactive antigens from infectious agents and foods resulted in MS and other autoimmune diseases being contracted by many of the individuals who were genetically susceptible to such diseases.

The identification of the likely causal factors of MS yields strategies for reducing disease risk and for controlling disease progression. MS prevention is best accomplished by ensuring that children receive adequate vitamin D and omega 3 EFA. Individuals with MS may be able to slow disease progression by avoiding foods that potentially yield cross-reactive antigens, by using strategies to ensure the integrity of the intestinal barrier and by consuming adequate vitamin D, omega 3 EFA, antioxidants and fibre. A decreased consumption of sugar, starch, omega 6 EFA and saturated fat would also be beneficial.

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