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Review Article

Evidence- Based Hypotheses about Levels of Prevention of Multiple Sclerosis: Current Findings, Future Prospects

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Abstract

To decrease the incidence of the costly and disabling multiple sclerosis, prevention of the disease or its complications by modulation of its evidence-based etiological or risk factors is the best strategy. Hereby, some evidences on the contribution of several factors in the pathogenesis of MS have been critically reviewed and some practical hypotheses for future investigations to confirm the validity of these factors as the bases for prevention of MS have been suggested.

Introduction

Multiple sclerosis (MS) is one of the most common diseases of the CNS [1]. Disease onset is typically between 20 and 40 years of age and the disease leads to considerable impairment in sensory, motor, autonomic, and cognitive function [1]. So the disease disables people at their most active years of youth [2].

Most of MS patients experience a relapsing-remitting (RR) clinical course; however, some neurological deficits may remain during remissions. Accumulation of these deficits is the reason that the clinical disease tends to be worsen during the course of MS in most patients. The currently prescribed medications are not ideally effective in halting this progressive deterioration [3,4] and are expensive. Diagnostic tests are costly too. Furthermore, a great amount of money is paid on rehabilitation and psychotherapy of patients. So, unfortunately, the burden of the disease on patient, his or her family and the society is considerably high [5,6].

The best way to diminish all these health and economic burdens is to prevent the development of the disease in healthy people and halt the progression of disabilities in patients. Like many other diseases, preventive medicine can offer a real prospect for future [7,8]. Disease prevention can be viewed in three levels, primary, secondary and tertiary. In primary prevention, *before* the disease emerges, some pre-clinical practical strategies are implemented to prevent the disease. Therefore, primary prevention reduces both the incidence and prevalence. Primary prevention is mechanistically based on understanding the etiologic base and precise analysis of risk factors for the diseases. In MS, a handful of these factors are proposed to prone people to disease although there are no confirmed etiologies.

Secondary prevention is used after the disease occurs, *but* the person is not aware of it. Magnetic resonance imaging (MRI) could help precocious diagnosis, but its practical use as a screening tool is debatable, expensive and mostly not accepted. There are no other screening tools feasible for early diagnosis of MS right now.

Third-level or tertiary prevention targets the person who already has symptoms of the disease. The goals of tertiary prevention are [1] to prevent future damage and pain secondary to the disease pathology, [2] to decrease the course of the disease progression [3] to prevent complications, [4] to care better for the patients and [5] to rehabilitate daily lives functions. Pertinent to MS, all these goals should be contemplated, although there are many overlaps between targets of tertiary prevention with the therapeutic targets assigned for pharmacotherapy, rehabilitation and psychotherapy. Currently, FDA-approved medications can only weakly decrease the track of deterioration of MS. Neuroprotective medications can help to achieve these goals. These neuroprotective medications are under study, but not yet approved. If these drugs can find their way to MS therapy, could be preventive at the third level. This is also the case of immunomodulatory drugs, if could effectively modify the course of the disease, can be accounted as third-level preventive medications.

Primary prevention is the most attractive level of disease prevention for MS. It is mechanistically based on understanding the etiology of the disease. Although the main features of MS were described clearly by Charcot in 1868, the etiology of this disease remains largely unknown [9]. The nomenclature of etiology of MS is not uncommon in the literature, however, considering the Koch's criteria of causation, there is no known etiology for MS [10]. If there were, the combat against the disease could be facilitated in terms of prophylaxis and pharmacological intervention. However, contribution of some predisposing risk factors to the pathogenesis cannot be denied in MS. We would like to call them "etiological factors" to emphasize on loyalty to Koch's definition as well as clarification that we respect current findings regarding their roles in predisposing people to MS or their contribution to the pathogenesis. These factors are not proven as causative elements. In fact, the synergistic effect of these factors might ultimately predispose a man to MS. Genetics and environments both are proposed as possible etiological factors [10].

Genetic Risk Factor: Can We Use Genetics for Prevention of MS?

Familial and heritability studies have suggested a role for genetics in MS [11,12]. According to these studies, MS does not result from gene mutations or aberrations; rather, polymorphisms in a number of genes may predispose people to MS. These polymorphisms act independently and each can contribute a little. Several studies have identified susceptibility genes on chromosome 6p21 and 17q22 in the coding regions for major histocompatibility complex class II (MHC II) [11-14]. Also the interleukin-7 receptor (IL-7R) gene alteration [15-17] and two single nucleotide polymorphisms within the interleukin-2 receptor alpha (IL-2Ra) coding region have been linked to MS risk [18]. Pathophysiologically, these polymorphisms might have effects on the immune system.

There is no doubt that genetics has revolutionized our understanding about the human diseases. Regarding MS, however, the practical application of these data has not been acquired yet. Gene screening for finding patients prone to MS, is neither ethical nor scientifically supported.

In another way, genetic engineering might find some ways to treat MS or prevent further worsening of the disease. This might work as a secondary or tertiary prevention strategy. Gene manipulation in cell therapy studies have been experimented in animal models. This type of investigations, not directly based on the mentioned genetic background of MS, shows the effects of administering genetically engineered cells in correction of some pathogenetic factors and is encouraging future studies [19]. However, strategies for correction of genetic deficits background in human MS seem far from realism, at least in accordance with our current knowledge and capabilities in gene-based therapies. So, currently there is no recommendation for gene manipulation techniques for MS therapy and prevention.

On the other hand the implication of genetic data on pharmacogenetics and pharmacogenomics of MS could be practically important in clinical neuropharmacology [20-23]. MS is a very personal disease with considerable inter- individual clinical variation, thus the personal features in response to and toxicity of drug treatments are important issues in MS therapy [24]. The genetic mechanisms of good response to or developing bad side effects during drug therapy in MS is extensively complex and largely unknown, although some attempts have been made to clarify them [25-27]. Studies focused on the origins of these heterogeneities in drug response can even contribute to our better understandings of the pathogenesis of MS.

Environmental Risk Factors: Any Hope for MS Disease Prevention?

Findings such as the little disease concordance of identical twins and geographic epidemiology, suggest that non-genetic or environmental factors are also involved in the etiology of MS. A number of environmental triggers have been studied including: viral infections, vitamin D deficiency and smoking and many others [28]. Some viral infections are among the most widely suspected non-genetic risk factors for MS. It is suggested that, in genetically predisposed individuals, exposure to certain viral infectious agents may lead to MS [10]. Involvement of several viruses has been postulated, but currently, the strongest evidence exists for Ebstain bar virus [EBV] [28]. Anyway, Koch's postulates regarding the four criteria designed to establish a causal relationship between a causative microbe and a disease cannot be applied to any virus for MS.

Despite what mentioned, EBV, have been associated with MS pathogenesis [29]. The mechanism for EBV contribution to disease triggering in genetically susceptible people, have not been explained yet. However, different pathomechanisms are theoretically suggested and/or experimentally explored, but most of them seem not to be conclusive. Direct infection of the CNS seems not to be a pathogenic mechanism underlying MS. In EBV- mediated syndrome, Infectious Mononucleosis, the direct invasion of the virus to the CNS is not common. In MS either, the presence of EBV in the neural tissues has not been shown in most studies. The penetration and accommodation of the B-cells hosting EBV to the CNS has been claimed to play a role as a target of immune-mediated CNS demyelination during reactivation of the virus but the concept remains unproven yet [29].

As an indirect effect of the virus, molecular mimicry between EBV and CNS antigens, transformation of the EBV-infected B-cells to immortalized memory cells with the potential of periodic secretion of myelin targeted auto-antibodies and antigen presentation by infected B-cells to CD4+ T-cells resulting in expansion of T-cells (with occasional cross reaction with the myelin auto- antigens) are proposed [30]. EBV binds to and enters into B cells, and gives them the opportunity to be immortalized. This interaction of EBV with B cells is mediated by the human complement receptor type 2 (CR2; CD21)[2]. The EBV-infected autoreactive B-cell might, in genetically susceptible individuals, cause autoimmunity. EBV-infected autoreactive B cells might also provide co-stimulatory survival signals to autoreactive T cells [31]. The disrupting effect of the virus on the Blood Brain Barrier [BBB] has been also suggested.

It has been proposed that elimination of EBV can prevent or modulate MS. However, trials targeting eradication of the EBV by antiviral treatments have shown controversial results in MS [32,33]. As a possible reason, cell-inhabiting viruses might escape from clearance by antiviral therapy. As we previously hypothesized [2], a possible strategy to treat MS might be eradicating B cells and ultimately the EBV safely hidden within these cells.

But to provide prevention strategy for MS, people could be vaccinated against EBV. This might also ultimately highlight the importance of this virus in susceptibility to MS. To develop a broad-spectrum vaccine against EBV and providing data on its safety and effectiveness is a critical step in this regard. The next step would be a well-controlled study to compare the incidence of MS between vaccinated people and those who have not received the vaccine. The protective effect of the EBV vaccine could then be evident.

In accordance with epidemiologic data, low blood level of vitamin D is a risk factor for the development of MS. Moreover, vitamin D serum level has been inversely associated with the severity and activity of the disease and progression of the clinical disability in patients [34]. However, controversial opinions exist regarding preventive and therapeutic benefits of administration of vitamin D in MS [8,35]. In animal studies on experimental allergic or autoimmune encephalomyelitis (EAE), vitamin D administration has been reported to be beneficial both prophylactically and therapeutically [36]. Increasing the serum level of vitamin D has revealed a beneficial effect on MS risk. In a prospective study on children after a first demyelinating attack, the risk to develop MS was inversely correlated with the vitamin D serum level. Also, higher vitamin D levels are predictive of a significantly lower risk of developing MS [36].

There are some lines of evidence that vitamin D has immunoregulatory functions. Based on this assumption vitamin D has been suggested to contribute to either pathogenesis or treatment of autoimmune diseases such as MS [37]. In MS pathophysiology, there are suspected effects attributable to vitamin D: (1) Involvement in modulation of the differentiation and function of antigen presenting cells, B cells and T cells, (2) shifting the cytokine network from a pro-inflammatory to an anti-inflammatory state, and finally, (3) potentiating the differentiation of regulatory T cells.

Some roles for vitamin D in the CNS are suspected too. A neuroprotective effect has been proposed for this vitamin, mechanistically related to regulation of neurotrophic factors [35].The interplay between genetic factors and vitamin D in MS pathogenesis and susceptibility has been proposed also [38].

Vitamin D is both safe and cheap. Therefore, it is logical to think that adjusting its serum level would be an acceptable preventive approach in both primary and secondary levels in MS. To confirm these issues, a large clinical trial for prevention of MS in a population can be designed. A sub-population supplemented with vitamin D could then be compared with those not receiving it, with the hope of recording a comparatively lower incidence of the disease in the former group. Alternatively, a longitudinal retrospective/prospective study in one population, before and after normalization of Vitamin D blood levels comparing MS incidence can give us valuable information in this regard. Clinical trials using vitamin D supplementation in MS patients are on-going and might shed more light on this hypothetical third-level prevention approach.

Smoking: A risk Factor Easy to Quit in Theory for Prevention of MS

Smoking has strong evidence of causality for MS. Several studies have suggested that there is an association between smoking and risk for MS. Most of current data have been extracted from prospective studies of MS risk and smoking including Nurses' Health Study, which revealed that smoking is associated with an increased risk of MS [39]. Relative incidence rate for women consuming 25 or more pack-years compared with non- smokers was higher. An increasing MS rate with increasing pack years was reported [40]. Several retrospective studies also confirm these results [41]. Moreover, smoking has similar effects on risk of other autoimmune diseases like lupus (SLE). In MS patients who currently smoke, it has been reported that the clinical course of MS is worse compared to non-smoker MS patients [41]. Smoking increases the risk of conversion from relapsing remitting to secondary progressive MS in patients suffering from MS. The mechanism explaining how smoking affects the susceptibility to and progression of MS is not known. It does not appear to be mediated solely by nicotine and components of cigarette smoke might also be important [42]. Nitric oxide, which is a component of smoke, may play some roles in demyelination and axonal loss [43] and so might contribute to susceptibility of smoking people to MS. Moreover, cigarette smoke has a well-established effect on the immune system [44].

Cessation of smoking is a behavior modification with no concern of adverse effects by its recommendation. It is clear that recommending people not to start smoking and quit if they smoke is a preventive strategy, not only for MS, but also for many other diseases. Furthermore, for preclinical and overt MS patients, cessation of smoking is a secondary and tertiary prevention strategy. Smoking is not easy to quit but if cessation is achieved, the prevention of MS is probably facilitated.

Conclusive Remarks

Contribution of several etiological or risk factors to the pathogenesis of MS is a reason for the complexity of MS pathogenesis. MS does not have classical etiologies to be used as bases for prevention, but evidence-based prevention using strategies to eliminate those risk factors is attractive to ultimately have a society with lower frequency of MS and less sever MS patients. Vaccination against EBV, normalization of vitamin D blood level and prohibition of smoking are among experimental strategies worth worldwide studying at all three levels of prevention of MS. Hopefully, we can have a better society with fewer disabled young people to live healthier and happier.

Conflict of Interest:

Not declared

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