

REVIEW ARTICLE

MULTIPLE SCLEROSIS – RISK FACTORS

10.36740/WLek202012122

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Multiple sclerosis (MS) is a chronic autoimmune condition of the central nervous system (CNS) affecting mainly young adult individuals. The prevalence ranges approximately between 50 and 300 per 100000 individuals. It is characterized by an inflammatory process, demyelination and axonal loss. Immunological mechanisms resulting in the damage to the myelin sheath effecting then in impaired nerve impulse conduction have the key role in MS pathogenesis. The role of inflammatory factors has also been proved. However, it has not been explicitly shown whether such an inflammatory process is the triggering factor or secondary to a yet unknown infectious factor or a degenerative process of the CNS. Therefore, recognition of the epigenetic risk factors, such as: geographical latitude, vitamin D level, hygiene hypothesis, Epstein-Barr virus (EBV) infection and others may contribute to better understanding of the mechanism underlying multiple sclerosis. Additionally, they may provide guidelines for more efficient therapies and better prevention of the disease. Aim of this review is to present most current data on multiple sclerosis risk factors, considering those less known.

KEY WORDS: risk factors, multiple sclerosis, genetic factors, environmental factors

Wiad Lek. 2020;73(12 p. I):2677-2682

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune condition of the central nervous system (CNS) affecting mainly young adult individuals. It is characterized by an inflammatory process, demyelination and axonal loss. The prevalence ranges between approximately 50 and 300 per 100 000 individuals which points to the incidence of about 2.3 million worldwide. The number may however be underestimated for the absence of data from such massive populations like China or India [1]. The course of the disease is variable (relapsing- remitting form, primary progressive, secondary progressive, primary progressive with exacerbations). The typical manifestations reported by the patients are: troubled sensation, impaired balance, troubled movement, impaired vision, sphincter disorders as well as impairment of cognitive functions [2]. At first the course of the disease may be subclinical which is proved by some of the specified manifestations a few years before the actual diagnosis as well as demyelination observed in the patients' MRI upon the clinical beginning of the clinical stage. Immunological mechanisms resulting in the damage to the myelin sheath effecting then in impaired nerve impulse conduction have the key role in MS pathogenesis [3]. The role of inflammatory factors has also been proved. However, it has not been explicitly shown whether such an inflammatory process is the triggering factor or secondary to a yet unknown infectious factor or a degenerative process of the CNS. Therefore, recognition of the epigenetic risk factors may contribute to better understanding of the mechanism which, concurrent to the genetic factors, underlies multiple sclerosis. Additionally, they may provide guidelines for more efficient therapies and prevention of the disease [4].

THE AIM

The aim of this review is to present most current data on multiple sclerosis risk factors, considering those less known.

REVIEW AND DISCUSSION**GENETIC FACTORS**

Higher prevalence of MS among certain ethnic groups and elevated risk of family history of the disease (the estimated risk for MS in the population ranges between 0.1 and 0.2%, however in first degree relatives of MS patients the risk grows up to 2.5 – 5% and may be influenced by sex) prove the role of genetic factors [4]. It was as early as in the seventies of the 20 c. that relation was first shown between the major histocompatibility

*complex (HLA) and the onset of MS. Multiple European studies proved that the presence of haplotype HLA-DR15 (allele DRB1 * 1501 and allele: DQA1 * 0102 and DQB1 * 0602) is associated with about threefold increase of the MS risk while the presence of HLA-A * 02 is directly associated with reduced risk of MS [5]. Moreover, studies of the whole genome (GWAS) pointed to over 200 loci of autosomal susceptibility beyond the major histocompatibility complex (HLA), including e.g. chromosome X variant. Most of such loci are found in the non-coding regions of the genome. They are thought to affect the regulation mechanisms and activity of the genes. What is more, many of them are common for other autoimmune diseases, such as type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus*

and Crohn's disease. It is estimated that genetic factors are responsible for 20% up to 30% of MS incidence, suggesting that the remaining inheritance is probably associated with epigenetic factors as well as gene-gene or gene-environmental factors relations [6].

ENVIRONMENTAL FACTORS AND LIFESTYLE

The growing body of evidence shows that multiple environmental factors and lifestyle have a role in development and course of MS. The major epigenetic factors contributing to MS are:

- Geographical latitude,
- Vitamin D level
- Hygiene hypothesis and infection with Epstein-Barr virus (EBV)
- Serological proof of cytomegalovirus (CMV) infection
- Exposure to tobacco smoke and organic solvents
- Childhood obesity
- Shift work
- Caffeine
- Alcohol
- Salt supply
- Intestinal microflora

GEOGRAPHICAL LATITUDE

Geographical coordinates are strongly related to the spread of multiple sclerosis as shown by less prevalent MS in tropical and sub-tropical zones. Migration studies carried out since the sixties of the 20 c. have illustrated that the risk of multiple sclerosis depends on the age of a migrating individual: people migrating from low risk countries (e.g. Australia, Israel) to high risk ones (e.g. Norway, other north European countries) before puberty (the assumed age of 15 years) show the risk similar to that represented by individuals who were born and live in high risk population [7] but exceptions in Mediterranean Europe and northern Scandinavia, and some systematic reviews, have suggested that the gradient may be an artefact. The authors sought to evaluate the association between MS prevalence and latitude by meta-regression. Methods and findings: Studies were sourced from online databases, reference mining and author referral. Prevalence estimates were age-standardised to the 2009 European population. Analyses were carried out by means of random-effects meta-regression, weighted with the inverse of within-study variance. The authors included 650 prevalence estimates from 321 peer-reviewed studies; 239 were age-standardised, and 159 provided sex-specific data. The authors found a significant positive association (change in prevalence per degree-latitude). Moreover, the prevalence of MS in second generation immigrants, originating from low risk countries was higher than among the first generation of immigrants. Recent extensive population study focused on the influence of immigration on MS risk in Ontario, Canada. The study comprised over 2.3 million immigrants among whom more than 1500 showed clinical manifestation of multiple

sclerosis already after immigration. This proved that the overall risk of MS was significantly lower in immigrants than in longtime residents, who are among populations showing the highest MS morbidity worldwide. The risk varied depending on the country of origin (higher in immigrants from Middle East and Western countries and lower in immigrants from East Asia). Moreover. The risk was higher in men than in women and the growth was proportional to the number of concomitant diseases. The study suggested possible growth of MS risk along with time of exposure to high risk environment which would prove the role of both, the age during migration and duration of stay in a given country [8].

EXPOSURE TO TOBACCO SMOKE AND ORGANIC SOLVENTS

There is a growing body of evidence proving that exposure to tobacco smoke (passive or active) may increase the risk of multiple sclerosis. The pattern of the relation is: the bigger the dose, the higher the risk [9]. Investigations evaluating cotinine, a biochemical marker of the use of tobacco, pointed clearly to the elevated level (≥ 10 ng / ml) prior to the onset of MS which may be associated with the risk increased by even 50%, particularly in young adults (<26.4 years) less adverse, nevertheless harmful, is passive exposure to tobacco smoke also increasing the risk of the disease. On the other hand, the oral use of tobacco and nicotine itself may take a protective part, considering the influence on $\alpha 7$ subunit of the acetylcholine receptor present on immune cells, suppressing then the receptor's activity [10]. The risk increase in consequence of exposure to smoke points to irritation of the lungs as a possible cause. Smoking activates the proinflammatory cells in the lungs and induces post-translation modification of proteins which may cross-react with the CNS antigens [11] gene-environment interactions may exert much stronger effects. In this study, we investigated potential interactions between genetic risk factors and smoking in relation to risk of developing multiple sclerosis. A population-based case-control study involving incident cases of multiple sclerosis (843 cases, 1209 controls). The mechanism comprising both, smoking and exposure to organic solvents as well as the risk for MS may underlie the proinflammatory profile of pneumonia. It is assumed that various sources of lung irritation may have a role in immunological response against modified own proteins or potentially autoaggressive cells present in the lungs and enhance development of multiple sclerosis in individuals genetically vulnerable to the disease [12] and a potential interaction between organic solvents and MS risk human leukocyte antigen (HLA).

HYGIENE HYPOTHESIS AND INFECTION WITH EPSTEIN-BARR VIRUS (EBV)

The hygiene hypothesis suggests that low exposure to pathogens during childhood, observed basically in the industrialized countries, may lead to higher risk of au-

toimmunological diseases and allergies at older age [13]. Elevated risk of multiple sclerosis in individuals representing high sanitary standards during early age was first reported in 1966 based on observations made by Leibowitz et al. Moreover, the reverse correlation between multiple sclerosis and the global spread of *Trichuris trichiura*, a common human parasite accepted as surrogate marker for infections with other parasites, along with low sanitary standards of a population, supported from the epidemiological standpoint the thesis of the role of hygiene in MS. This hypothesis enhanced numerous investigations aimed at identification of infectious factors taking part in multiple sclerosis. Widely described in literature is Epstein Barr virus increasing the risk for MS [14]. Practically omnipresent, EBV is the cause of pediatric infections in low- and medium-income countries. Resulting of seropositivity in 3-year old children, it is transmitted mainly through saliva and after infection remains latent due to B lymphocytes. The studies showed that infection with EBV seemed to be a necessary, however insufficient, condition for MS. EBV seroprevalence is higher in MS patients (the higher the antibody titre, the greater the risk for MS) [15].

It has also been shown that symptomatic EBV infection (with IgM antibodies) is more prevalent in patients with multiple sclerosis. The most striking observation was however the serological conversion of originally EBNA1 negative patients into positive ones prior to MS onset [16]. It seems also that EBV infection during puberty or later is associated with higher risk for MS than infection undergone during childhood. It has also been proved that EBNA1 antibodies titre interacts with HLA genetic risk variants while infectious mononucleosis interacts with HLA DRB1 * 15: 01 increasing the risk for multiple sclerosis [17]. There is therefore strong evidence supporting the role of EBV in pathophysiology of MS.

SEROLOGICAL PROOF OF CYTOMEGALOVIRUS (CMV) INFECTION

Together with Epstein-Barr virus, CMV belongs to the same family of herpesviruses. In adults infections are usually asymptomatic while CMV seroprevalence grows in a nearly linear way along with age [18].

Earlier studies showed no relation between seropositivity and the risk for multiple sclerosis. Nevertheless, some recent investigations suggest that in CMV patients (seropositivity) the prevalence of conversion to MS is reduced following the first neuroinflammatory flare-up. However, the cause for potential protective role of CMV remains unclear and speculative [19].

VITAMIN D LEVEL AND SUN EXPOSURE

Evidence suggests that increased exposure to ultraviolet radiation has a protective role against multiple sclerosis. The major mediator of the process is vitamin D - a pro-hormone, member of fat-soluble vitamin group. Responsible first of all for homeostasis, it also takes part in

bone formation [20]. The major sources of vitamin D are diet (fat fish, e.g. mackerel) and supplementation while the largest part of the demand is covered by photochemical transformation into the active form (1 α ,25-dihydroxycholecalciferol) in the triggered in the skin by UV-B radiation. 25-OH-D concentrations vary depending on the target population. The present accepted target range of 25-OH-D to ensure immunological health and generally for the patients is 30–60 ng / ml [21]. It is recommended to increase serum vitamin D before 20 years of age which reduces remarkably the risk for MS. This may be due to puberty, the most sensitive period during which vitamin D develops the immunomodulatory effect and cerebral development enters its final stage. The protective role of vitamin D was also proved by some later studies of its supplementation. Given the geographical latitude, smoking habits and obesity, the relative risk for multiple sclerosis in women receiving vitamin D at continuous dose of 400 IU /day was by 40% lower than in females who did not take any additional vitamin D [22]. Exposure to sunlight and diet rich in fat fish also contribute to the lowered risk. There are multiple potential mechanism underlying the effect of vitamin D on MS. The genetic studies revealed that lowered levels of 25(OH)D strongly correlated with higher risk for MS. Moreover, it was observed that the risk for MS is associated with the enzyme coding gene activating vitamin D (CYP27B1) and the genetic variant rs703842 in CYP27B1 in Caucasian population [23]. It was also shown that vitamin D may regulate genes of the immunological system which have a role in development of MS. The molecular investigations indicates that the multiple sclerosis loci were enriched with VDR binding sites, including the HLA-DRB1 promotor region [24]. Vitamin D shows also the immunological effect upon the inflammatory stage of MS. All the studies listed emphasize the role of vitamin D in reduction of the risk for MS.

CHILDHOOD OBESITY

Throughout the last decades the figures for pediatric obesity tripled and now it is known to be associated with a general inflammatory disorder (through adipokines). There is also a growing body of evidence supporting the role of obesity in increased risk for multiple sclerosis. Extensive cohort studies evaluating the effect of obesity during puberty on future risk for MS in women confirmed such hypothesis [25]. A correlation was also observed between the body mass index (BMI>27) and the relative risk for multiple sclerosis in girls with obesity and severe overweight. In adults the relation is less obvious. The time window when the effect of obesity upon MS is strongest is the period of puberty – around 10 years of age [26]. The authors describe at least several possible mechanisms leading to increased risk for MS in young obese individuals. First of all, the occurrence of a low-level inflammatory condition and the presence of leptin, associated with obesity, increase the level of pro-inflammatory mediators in the fatty tissue. Obesity is also the cause of reduced bioavailability of vitamin D,

additionally promoting the inflammatory processes. Both mechanisms may enhance activation of adaptive, auto-reactive immune cells which may trigger a neurological inflammation in multiple sclerosis [27].

SHIFT WORK

The up-to-date investigations showed that shift working, particularly the late shift, increases the risk for autoimmune diseases, including multiple sclerosis. Two major studies showed that the shift system increases the risk for MS in young people (about 20 years of age) by approx. 1.7 times. In individuals older than 20 the correlation is not that strong [28] 1.08–1.34, $p=0.001$. Working at night results in disturbances of the circadian rhythm, lack of sleep and suppression of melatonin. The latter suppresses differentiation of T lymphocytes into pathogenic Th17 as shown during in vitro studies carried throughout several molecular cycles [29]. The clinical studies revealed that based on blood melatonin, it was possible to prognose intensity of MS and also that exogenous melatonin decreased the inflammatory response in MS patients. What is more, a recent study comprising nurses working on shift basis added some information about duration of the late shifts. It suggested that long-time (over 20 years) exposure to frequent (≥ 3 nights/month) late shifts may have a role in pathogenesis of MS. Apart from night working, also other circadian sources and sleep disturbances (e.g. light at night, use of screens by teenagers and young adults) may have a role in development of multiple sclerosis, particularly in predisposed individuals [30].

The effect of a diet; caffeine, alcohol, consumption of salt.

CAFFEINE

Coffee contains more than a thousand of biologically active substances, including caffeine stimulating the central nervous system [31]. Having the antagonizing effect on adenosine receptors present in neurons and glial cells, caffeine binds also with macrophage adenosine receptors to change polarization from “pro-inflammatory” phenotype (M1) to “anti-inflammatory” phenotype (M2). The adenosine receptor A1 is found also on peripheral blood mononuclear cells (PBMC) which regulate pro-inflammatory signaling for TNF α and secretion of IL-6. Blood samples from patients with multiple sclerosis showed reduced serum adenosine and adenosine A1 as well as smaller number of PBMC receptors; activation of adenosine caused also no suppression of TNF α . A later study confirmed such results revealing that patients with MS showed lower expression of A1-adenosine receptor [32].

To sum up, persons who reported high consumption of coffee (> 900 ml daily) showed the risk for multiple sclerosis reduced by ~ 30% [31].

CONSUMPTION OF SALT

High consumption of salt is among numerous eating habits which emerged throughout the last half-century. Nowadays adults consume over tenfold of the physiological demand

for salt. The carried out studies and in vitro experiments point explicitly to the relation between excessive supply of salt and increased risk for MS. The underlying mechanism is activation of kinase 1, promoting differentiation of lymphocytes T into pro-inflammatory Th 17. This was proved by later experimental models of MS in mice, where high salt diet enhanced vulnerability of mice to multiple sclerosis and increased the number of future exacerbations [33].

ALCOHOL

It has been accepted that multiple sclerosis is reversely correlated to consumption of alcohol, depending on the dose, as proved by epidemiological studies. One of the studies reported that Danish women representing low consumption of alcohol showed risk for MS by 44% lower than non-drinkers. This was proved also among male population although the results were not equally strong [34] 5,4'-trihydroxy-trans-stilbene. Multiple studies concerned consumption of wine, particularly red, containing resveratrol. Showing the anti-oxidative effect, it prevents and inhibits chronic diseases, reduces all-cause mortality and improves the overall health condition. Resveratrol was tested in multiple EAS MS rodent models to show increased remyelination and lowered level of pro-inflammatory cytokines. Observations pointed also to improved dysfunction of mitochondria and reduced oxidative burden. Another potential mechanism underlying the effect of resveratrol is induction of apoptosis or promotion of phenotype change into regulatory Th17. The change results in reduction of the overall serum level of pro-inflammatory cytokines: IL-12 and IFN- γ [35].

INTESTINAL MICROFLORA

Humans are colonized by innumerable microbiological factors, such as fungi, viruses, bacteria and eukaryotic organisms, found on mucosa and the skin, which may act as modulators of autoimmunization. The studies carried out so far suggested interaction between intestinal bacteria and cells of the immunological system, both congenital and acquired [36]. It was shown that changes in microflora of intestinal compartments impaired the balance between inflammatory conditions and regulation of the host immunological response (interaction with lymphocytes and dendritic cells in lamina propria of the GI tract. It was also observed during tests on transgenic mice that following fecal microbiota transplantation from a MS patient to the mice model (healthy subject), autoimmunization was more frequent compared to situation when microbiome from a person other than diagnosed with MS was transplanted to a twin mice model. The results may be explained by different composition of microbiome from patients with MS, triggering a pro-inflammatory response in vitro [35].

CONCLUSIONS

Despite differences in prevalence of multiple sclerosis, resulting for example from geographical factors, the environmental and genetic factors are sure to have a role in development of the dis-

ease. What is more, the number of such factors is continuously growing. Moreover, the chronic course of the disease makes it possible to affect long-time disability. Therefore better recognition of such consequences for development and evolution of multiple sclerosis may bring in future some improvements in prevention and optimization of the patient care. Patients diagnosed with multiple sclerosis should be educated in this respect which could facilitate modification of their lifestyle.

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Conflict of interest

The Authors declare no conflict of interest.

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Received: 17.10.2020

Accepted: 03.12.2020

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D – Writing the article, **E** – Critical review, **F** – Final approval of the article