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SIGNIFICANCE OF INTERACTIONS BETWEEN GENETIC AND ENVIRONMENTAL FACTORS IN ETIOLOGY OF MULTIPLE SCLEROSIS

ZNAČAJ INTERAKCIJA GENETSKIH I SREDINSKIH FAKTORA U ETIOLOGIJI MULTIPLE SKLEROZE

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Abstract

Multiple sclerosis (MS) is an immune-mediated disorder of central nervous system. It most frequently occurs in young female adults, and the prevalence increases with latitude. So far, over 200 genes, loci and single nucleotide polymorphisms (SNPs) have been linked with MS, although each one contributing only slightly in the overall etiology of the disease. The *HLA-DRB1*15:01* haplotype has been shown to have the strongest association with MS occurrence risk in genome-wide association studies (GWAS), while *HLA-A*02* has been shown to have a protective effect. The exact etiology of MS is still unclear, but there seems to exist an interplay between genetic burden of an individual, and environmental factors which contribute to MS occurrence such as Epstein-Barr virus (EBV) infection, vitamin D levels, smoking status, and early life obesity. An interaction between *HLA-DRB1*15:01* and EBV infection, the strongest environmental risk factor for MS, has been observed. It has been suggested that this interaction is a result of *HLA-DRB1*15:01* acting as a coreceptor for EBV, thus providing a pathophysiological explanation connecting environmental with genetic MS risk factors. A recent study including participants from two case-control studies with over 13.000 individuals showed that an interaction exists between sun exposure, vitamin D levels, and *HLA-DRB*15:01* carrier status, leading to increased risk of MS in individuals with lower sun exposure, vitamin D deficient, and *HLA-DRB*15:01* positive. The interaction of *HLA-DRB1*15:01* with smoking has been observed in a meta-analysis, while the same study only showed an interaction of smoking with the absence of *HLA-A*02* in a subset of studies. The risk of MS has been shown to vary in obese individuals, with obese individuals with the susceptible genotype (*HLA-DRB1*15:01+, HLA-A*02-*) having 16x higher odds of having MS compared with non-obese persons with a non-susceptible genotype.

Keywords:
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Sažetak

Multipla skleroza (MS) je imunološki posredovan poremećaj centralnog nervnog sistema. Najčešće se javlja kod mladih odraslih žena, a prevalencija raste sa geografskom širinom. Do sada je preko 200 gena, lokusa i jednonukleotidnih polimorfizama (SNP) povezano sa MS, iako svaki od njih samo neznatno doprinosi sveukupnoj etiologiji bolesti. U studijama asocijacija na nivou genoma (GVAS) pokazalo se da haplotip *HLA-DRB1*15:01* ima najjaču povezanost sa rizikom od pojave MS, a *HLA-A*02* ima zaštitni efekat. Tačna etiologija MS je još uvek nejasna, ali izgleda da postoji interakcija između genetskog opterećenja pojedinca i faktora sredine koji doprinose nastanku MS, kao što je infekcija Epštajn-Barovim (*Epstein-Barr*) virusom (EBV), nivo vitamina D, pušački status i gojaznost u ranom životnom dobu. Primećena je interakcija između *HLA-DRB1*15:01* i EBV infekcije, najjačeg sredinskog faktora rizika za MS. Pretpostavlja se da ova interakcija nastaje usleg toga što *HLA-DRB1*15:01* deluje kao koreceptor za EBV, čime se pruža patofiziološko objašnjenje koje povezuje faktore sredine sa genetskim faktorima rizika za nastanak MS. Nedavno sprovedena studija, koja je uključivala učesnike iz dve studije slučajeva i kontrola sa preko 13.000 uključenih ispitanika, pokazala je da postoji interakcija između izlaganja suncu, nivoa vitamina D i *HLA-DRB*15:01* statusa, sa povećanim rizikom od nastanka MS kod osoba sa nižom izloženošću sunčevim zracima, deficitom vitamina D i pozitivnim *HLA-DRB*15:01*. Interakcija *HLA-DRB1*15:01* sa pušenjem pronađena je u metaanalizi, dok je ista studija pokazala interakciju pušenja sa odsustvom *HLA-A*02* samo u podskupu uključenih studija. Pokazalo se da rizik od MS varira kod gojaznih pojedinaca, pri čemu gojazne osobe sa podložnim genotipom (*HLA-DRB1*15:01+, HLA-A*02-*) imaju 16 puta veće šanse za MS u poređenju sa osobama koje nisu gojazne sa genotipom koji nije podložan.

Ključne reči:
multipla skleroza,
interakcija,
genetika,
faktori rizika,
revijal

Introduction

Multiple sclerosis (MS) is an immune-mediated disorder of the central nervous system (1). It is the most common non-traumatic cause of disability in young adults (2). Clinical presentation of MS varies significantly between individuals,individuals; however, it has been established that three distinct disease phenotypes exist in MS: relapsing-remitting multiple sclerosis (RRMS), primary progressive multiple sclerosis (PPMS), and secondary progressive multiple sclerosis (SPMS) (3). The most commonly diagnosed phenotype in 85% of patients with multiple sclerosis (PwMS) is RRMS, in which there exists an alteration between periods in which no new neurological symptoms occur (remissions), and periods in which new neurological symptoms occur, or existing ones worsen (relapses) (4,5). The cornerstone of MS treatment is disease-modifying therapy (DMT); alongside glucocorticoids (first-line treatment), plasmapheresis, and IV immunoglobulin (second-line treatment) for treatment of acute exacerbations (6).

Worldwide, there are 2.9 million people living with MS in 2023 (5). Risk of acquiring MS is different in different population groups. It affects mostly young adults, with an average age at diagnosis of 32 years (5). Multiple sclerosis occurs more frequently in women, and the risk of acquiring MS increases with latitude (5,7). The observed increase of risk with increasing latitude can be explained by the deficit of vitamin D at higher latitudes, which has been shown to be an important environmental risk factor for developing MS along with smoking, Epstein-Barr virus (EBV) infection, and early life obesity (8-10).

The influence of genetics on MS risk has been established. Concordance rates of 25 - 30% for monozygotic twins, and 3-5% for dizygotic twins have been reported (11). The lifetime risks for developing MS for first-degree relatives of PwMS have been estimated at 3 - 5%, which amounts to relative risks of 15 - 25 when compared to the general population which has a lifetime risk of 0.2% (12). However, only in 11.8% of cases PwMS have a family member diagnosed with MS – familial multiple sclerosis, as opposed to the majority of cases being sporadic (13). The exact etiology of MS is still unclear, but there seems to exist interplay between environmental factors, and the genetic burden of an individual.

Interplay between genetic and environmental factors

So far, over 200 genes, loci and single nucleotide polymorphisms (SNPs) have been linked with MS, although each one contributing only slightly in the overall etiology of the disease (14). The *HLA-DRB1*15:01* haplotype has been shown to have the strongest association with MS occurrence risk in genome-wide association studies (GWAS), while *HLA-A*02* has been shown to have a protective effect independent of *HLA-DRB1*15:01* (15,16). Homozygosity for *HLA-DRB1*15:01* has been associated with threefold increase of risk of MS (15).

Different environmental factors have been studied in an attempt to discern the etiology of MS, and a different level of evidence has been obtained for different risk factors, with smoking, EBV infection, deficit of vitamin

Table 1. Environmental risk factors for MS

Factor	OR	HLA gene interaction	Combined OR (nongenetic factor + HLA allele)	Immune system implied	Level of evidence
Smoking	1.6	Yes	14	Yes	+++
EBV infection (seropositivity)	3.6	Yes	15	Yes	+++
Vitamin D level < 50 nM	1.4	No	NA	Yes	+++
Adolescent obesity (BMI > 27 at age 20 years)	2	Yes	15	Yes	+++
Low sun exposure	2	No	NA	Yes	++
Infectious mononucleosis	2	Yes	7	Yes	++
Passive smoking	1.3	Yes	6	Yes	+

Modified according to Olsson et al. (17)

D, and adolescent obesity being the leading environmental risk factors (**table 1**) (17).

Interaction with EBV

Infection with EBV, the causative agent of infectious mononucleosis (IM) has been shown to be associated with MS occurrence, with the risk being increased in individuals even 30 years after the infection with IM (18-20). However, recent studies have emphasized the influence that EBV infection has on MS development, implicating that EBV infection has a causative role in the majority of MS cases (21,22). Namely, in a cohort study including more than 10 million US military personnel, it was shown that EBV seroconversion occurred in 97% of persons who were seronegative at the baseline and developed MS in the course of the follow-up, as opposed to 57% conversion rate in persons who didn't develop MS, with a hazard ratio of 32.4 (21). There are no known or theoretical factors of enough strength which could confound the stated results, implying the key role of EBV infection in the MS occurrence (21,23).

Interactions between genetic determinants of MS and EBV infection have been observed (24). An earlier study showed an interaction effect between *HLA-DRB1*15:01* presence, *HLA-A*02* absence, IM and increased MS risk, with findings remaining robust after stratification for smoking status (25). Experimental evidence of interaction between *HLA-DRB1*15:01* and EBV has since been obtained in mice (26). Most recently, it has been suggested that this interaction is a result of *HLA-DRB1*15:01* acting as a coreceptor for EBV, thus providing a pathophysiological explanation connecting environmental with genetic MS risk factors (27). All of the stated above implicates that EBV has an essential role in MS pathogenesis, signaling a potential for future preventive measures directed at the viral agent.

Interaction with vitamin D

There is evidence from prospective cohort studies that vitamin D deficiency plays a role in MS development, a finding further supported by the observation that MS incidence increases with latitude (7, 28, 29). Vitamin D also plays a role in relapse occurrence, with relapses occurring more frequently in individuals with reduced levels of vitamin D in serum (30). There is an apparent interaction between vitamin D and several genes recognized as risk factors in MS, including *HLA-DRB*15:01* (31, 32). A recent study including participants from two case-control studies with over 13.000 individuals showed that an interaction exists between sun exposure, vitamin D levels, and *HLA-DRB*15:01* carrier status, leading to increased risk of MS in individuals with lower sun exposure, vitamin D deficient, and *HLA-DRB*15:01* positive (33). Interestingly, the same study showed no interaction between *HLA-A*02* absence and vitamin D deficiency (33). Also, it has been observed that the overlapping of DNA binding sites between EBV and vitamin D exist, which leads to vitamin D outcompeting EBV in individuals with high levels of vitamin D, explaining the inverse correlation found between EBV and levels of vitamin D (34, 35). Vitamin D deficiency apparently has a very important role in MS development, which opens the possibility for prevention by timely supplementation in cases where a deficit exists.

Interaction with smoking

The lifestyle factor most associated with increased MS risk is smoking, with population attributable fraction of smoking for MS of 13% (36-38). The mechanism by which smoking contributes to MS risk still remains uncertain, but the results of some studies suggest that smoking increases the already existing genetic susceptibility in persons with *HLA-DRB1*15:01* and with absence of *HLA-A*02* (39, 40). The degree to which smoking along with EBV infection interacts with the genetic risk profile in MS still remains unclear, with studies performed so far providing conflicting results (41, 42). However, the interaction of *HLA-DRB1*15:01* with smoking has been observed in a meta-analysis, while the same study only showed an interaction of smoking with the absence of *HLA-A*02* in a subset of studies (43). Smoking remains one of the most easily preventable lifestyle factors associated with MS, and the burden of the disease could be lessened with adequate primary prevention strategies, which is also true for many other non-communicable diseases.

Interaction with obesity

Obesity in adolescence has been shown to be a risk factor for MS development in observational studies

(44-46). Mendelian randomization studies have been performed in an attempt to reduce possible bias, confirming these findings (47,48). The risk of MS has been shown to vary in obese individuals, depending on their genetic burden (*HLA-DRB1*15:01* and *HLA-A*02* carrier status), with obese individuals with the susceptible genotype (*HLA-DRB1*15:01+*, *HLA-A*02-*) having 16x higher odds of having MS compared with non-obese persons with a non-susceptible genotype (49). A most recent GWAS has identified the existence of shared risk SNPs between MS and obesity, and a shared functional gene *GGNBP2* between MS and obesity, paving the road to further studies which could clarify the manner and extent in which obesity plays a role in MS pathogenesis (50). Similarly to previously stated findings regarding vitamin D and smoking, an interaction was observed between adolescent obesity and EBV infection, with persons with obesity and past IM having an almost 15 times higher odds of having MS compared with persons without these two risk factors (51). Further studies demystifying exact role of obesity in MS development are necessary.

The potential for prevention

Primary prevention points

Recent breakthroughs in understanding the pathogenesis of MS indicate a realistic potential for primary prevention, with the focus on preventing exposure to environmental factors. The results of the US army cohort study mentioned previously indicate that prevention of EBV may play a key role in MS prevention (21). Bearing in mind the ubiquitary nature of EBV, with 50% of population being seropositive at age 5 - 9 in developed countries, and 90% in developing countries, childhood vaccination against EBV will be necessary in order to prevent the infection with this virus (52). So far, there are no licensed EBV vaccines, and there are several clinical trials ongoing, however, the results of early studies so far have succeeded in preventing IM, but not EBV infection, which may be insufficient to prevent MS (53,54). The other gateways for prevention include supplementation of vitamin D in patients with low serum levels (< 50 nmol/L), which could reduce the risk of MS by more than 60%, preventing early life obesity, which could eliminate around 15% of cases, and smoking cessation which could prevent around 8% of cases of MS (55,56).

Secondary prevention

Population based studies of newer date have shown the presence of what appears to be a prodromal phase in MS (57,58). The results of these studies indicate that the prodromal phase is detectable 5 years before MS symptoms onset, and possibly even up to 20 years in patients who develop PPMS (56). It appears that numerous symptoms and signs which do not occur in healthy populations appear in MS prodrome, such as cognitive disorders, pain, fibromyalgia, bowel issues, bladder issues, and other (56). These findings indicate the potential for early detection and secondary prevention of MS, if adequate biomarkers are found, seeing how the signs and symptoms of the prodrome are non-specific.

Conclusion

Even though significant breakthroughs have been made in the past couple of years in understanding the etiology of MS, there are still numerous unknowns, especially regarding the level of influence of each of the risk factors on the pathogenesis of the disease, and the precise degree in which their interactions enhance the risk of developing it. Further studies with more complex models, encompassing more risk factors alongside the genetic profile will be necessary in order to fully understand MS. From what is understood so far, it appears that the key to preventing MS will lie in preventing exposure to environmental risk factors, with EBV vaccination being the crucial moment in prevention of this disease.

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