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# Environmental Risk Factors and Gene-Environment Interactions for the Development of Multiple Sclerosis

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## Introduction

Multiple Sclerosis (MS) is an inflammatory demyelinating autoimmune disorder of the Central Nervous System (CNS). The typical disease course is Relapsing-Remitting (RR) MS and treatment with Disease Modifying Treatment (DMT) should be initiated as soon as possible following a diagnosis of relapsing MS for individuals with a first clinical event and MRI features consistent with MS, in whom other possible causes have been excluded. Patients with MS tend to do not completely recover from relapses with steroid pulse therapy after 5 to 10 years disease duration and develop to Secondary Progressive (SP) MS. It is now well accepted that MS is not only a demyelinating disease in white matter but neurodegenerative disorder that affect axonal and neuronal damage from the beginning.

In this article, I provide an overview of the trend of recent studies of MS pathogenesis and discuss how gene-environment interaction may affect the course of MS.

## Inflammatory Cascade in MS

According to THE USE OF DISEASE-MODIFYING THERAPIES IN MULTIPLE SCLEROSIS, the mechanism of MS, which is presented at ECTRIMS/ACTRIMS in Boston, from September 10th to 13th in 2014, is reviewed as follows [1].

The etiology of MS is still unresolved but inflammatory cascade in both peripheral and Central Nervous System (CNS) are important and various classes of immune cells (including macrophages, natural killer cells and others) as well as certain lymphocytes populations are thought to be involved [2]. CD4+ and CD8+ T cells are activated in the peripheral lymphoid tissues. Antigen presentation to naïve CD4+ T cells causes differentiation into Th1, TH17, Th2 and regulatory T cells, depending on the antigen presented the cytokines environment and the presence of co-stimulatory molecules [2-4]. There is a bias towards Th1 and Th17 environment with T regulatory dysfunction that allows inflammation to predominate [5]. Secreted cytokines and matrix metalloproteinases disrupt the blood brain barrier [6].

This disruption, along with up-regulation of adhesion molecules on blood vessel endothelium and activated T cells, allows T cells to gain entry into CNS, where additional activation takes place that initiates an inflammatory and damaging cascade of events within the CNS (Table 1). Multiple inflammatory cells become involved, including microglia cells, and macrophages. In addition to CD4+ T cell activation, CD8+ T cells have also been identified as important contributors to damaging CNS inflammation, and have been identified as the predominant T cell present in active MS lesions [7].

**Table 1:** Inflammatory cascade in multiple sclerosis [1].

| BBB (Blood Brain Barrier) | |
|---|---|
| **Periphery** | **CNS** |
| 1. Antigen presentation to CD4+ prompting activation and proliferation of inflammatory T cells (Th1 and Th17)<br>2. Secretion of pro-inflammatory cytokines<br>3. Up-regulation of adhesion molecules<br>4. Disruption of blood brain barrier<br>5. T cell migration into CNS<br>6. B cell activation, proliferation and migration into CNS<br>7. Inadequate T regulatory function | 8. Presentation of CNS Antigen to T cell with reactivation<br>9. Recruitment of other inflammatory cells : CD 8+, B cells, monocytes, macrophages, microglia<br>10. Damage to myelin, oligodendrocytes and axons resulting from: cytokine damage, Ab activity, complement damage, oxidative stress mitochondrial dysfunction |

Further contributors to CNS damage in MS are associated with B cell activation. B cells function as antigen presenting cells and also produce antibodies that have damaging effects on myelin, oligodendrocytes and other neuronal structures [8].

Recent studies have also revealed that mitochondrial damage (possibly as a result of free radical, reactive oxygen species and Nitrous Oxide (NO) activity associated with activated microglia) and iron deposition occur in MS and make a significant contribution to demyelination and oligodendrocyte and damage [9-11].

Immune-mediated responses leading to inflammation, with secretion of inflammatory cytokines, activation of microglia, T and B cell activity, mitochondrial damage and inadequate regulatory function, are believed to be at least partially responsible for demyelination, oligodendrocyte loss and axonal damage. Axonal loss, which correlates best with disability, occurs early in the disease process as evidenced by identified pathological changes as well as imaging studies [12,13].

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## Environmental Risk Factors in MS

### Smoking

Cigarette smoke contains many mutagens which potentially may affect long lasting immunity; a recent review indicates that smoking generally leads to an immunosuppressant state [14]. The higher expression of MMPs in smokers could be advantageous for immune cells to cross the Blood Brain Barrier (BBB) to the CNS parenchyma. It is noteworthy that a comparison of MRI scans from smokers and non-smokers with MS showed more contrast enhancing lesions among the smokers, which suggests an increased breakdown of the BBB [15].

### Microbiome

The importance of the microbiota in various bodily functions is becoming more apparent. As well as bowel-related disease, the gut microbiome is playing a role in metabolic and autoimmune disorders. As an exploratory study Mowry et al. reported that they have found a decrease in *Faecalibacterium* abundance in MS patients compared with controls from fecal samples of 15 subjects (seven MS patients and eight healthy controls) [16].

At ECTRIMS/ACTRIMS 2014 meeting in Boston, Tremlett et al. reported about gut microbiome in early pediatric MS as a case-control study. They have surveyed about gut microbiome of 20 very early onset children with MS (<2 years disease duration) and 14 controls {age range: 4-18 yrs.}. What they have found was specific bacteria taxa were significantly altered in relative abundance between MS cases compared with controls ($p<0.05$); 4401 taxa were depleted and microbiome composition was influenced by disease modifying drug exposure and race. (Posters (P) 615, Tremlett et al.) Ghandi et al. reported that gut microbiome was linked to immune cell phenotype in MS. (P616, Ghandi et al.)

### Vitamin D and Others

Epidemiological and experimental data suggest that vitamin D deficiency is associated with an increased risk of developing MS [17]. Immuno-modulatory changes during pregnancy lead to amelioration of Th1-type autoimmune diseases, such as MS and rheumatoid arthritis, but after the delivery the disease activity often returns [18]. Jalkanen et al. reported that the prevalence of vitamin D deficiency (< 50 nmom/l) during pregnancy was high (73%) among MS patients [18]. Vitamin D levels were significantly higher during pregnancy when compared to early post-partum values among MS patients. At the end of the follow-up period, the vitamin D levels returned to levels of observed early pregnancy. They have concluded that Vitamin D deficiency during the pregnancy and lactation seems to be common in mothers with MS and needs to be treated adequately [19].

At ECTRIMS/ACTRIMS 2014 meeting, Assessment of Iron deposition pattern in MS and NMO lesions with ultra-high field quantitative susceptibility mapping was reported. (Parallel Sessions (PS) 2.4, Chawla et al.) MS deep grey matter: the relation between demyelination, neurodegeneration, inflammation and iron (Young Investigators Session (YI) 1.5, Fischer et al.) and a link between neuronal degeneration and white matter demyelination in MS: vascular supply (PS11.6, Haider et al.) were also reported [9].

## Genetic Risk Factors in MS

Although the regular population risk of MS is as low as 0.1%, the sibling risk of MS is 2～4% and the risk of MS among monozygotic twin is as high as 30%. The major histocompatibility complex (MHC) region is strongly associated with MS susceptibility. HLA-DRB1*15:01 has the strongest effect, and several other alleles have been reported at different levels of variation. Using SNP data from genome-wide studies, Patsopoulos et al. imputed and tested classical alleles and amino acid polymorphism in 8 classical Human Leukocyte Antigen (HLA) genes in 5,091 cases and 9,595 controls. They identified 11 statistically independent effects overall: 6 HLA-DRB1 and one DPB1 alleles in class II, one HLA and two B alleles in class I, and one signal in a region spanning from MICB to LST1 [20].

Using the ImmunoChip custom genotyping array, International Multiple Sclerosis Genetics Consortium (IMSGC) analyzed 14,498 patients with MS and 24,091 healthy controls for 161,311 autosomal variants and identified 135 potentially associated regions (p-value $<1.0x10^{-4}$). In a replication phase, they combined these data with previous Genome-Wide Study (GWAS) data from an independent 14,802 patients with MS and 26,703 healthy controls. In these 80,094 individuals of European ancestry they identified 48 new susceptibility variants (p-value $< 5.0x10^{-8}$); three found after conditioning on previously identified variants. As a conclusion, there are now 110 established multiple sclerosis risk variants in 103 discrete loci outside of the Major Histocompatibility Complex [21].

At ECTRIMS/ACTRIMS 2014 meeting in Boston, several new results were reported as late braking posters. Exome sequencing unravels novel candidate genes in familial MS. (Late Breaking Posters (LBP) 18, Melamed et al.). Pathogenic mutations and risk alleles in familial MS were identified (LBP22, Vilarino-Guel et al.). Low-frequency coding variation in PRF1 and GALC identifies a number of MS risk genes in both known risk loci and elsewhere in the genome. These effects account for a small but significant proportion of disease risk heritability and reveal novel risk genes and aspects of MS susceptibility biology (LBP4, Cotsapas et al., IMSGC).

## Gene-Environment Interactions for the Development of MS

Aspects of immune functions are promoted by cigarette smoking and genetic studies indicate an interaction between smoking and genes that regulate immune function [22]. Briggs FB et al. studied whether variation in genes involved in metabolism of tobacco smoke constituents may modify MS risk in smokers [22]. They reported that tobacco smoke exposure at the age of 20 years was associated with greater MS risk in both data sets (in California, odds ratio [OR]=1.51 {95% confidence interval (CI)=1.17-1.9}; in Sweden, OR=1.35[1.40-1.74]). A total of 42 NAT1 variants showed evidence for interaction with tobacco smoke exposure ($P_{corrected}$ <0.05) [23].

Interaction between exposure to heavy metals and MS-associated genes was studies by Napier et al. They explored the relationship between environmental exposures to lead, mercury, and solvents with 58 Single Nucleotide Polymorphism (SNPs) in MS-associated genes. Data from a population-based case-control study of 217 prevent MS cases and 496 age-, race-, gender-, and geographically-matched controls were used to fit conditional logistic regression models of the association between the chemical, gene, and MS, adjusting for education and ancestry. MS cases were more likely to report exposure to lead (adjusted OR (AOR) = 2.03; 95% CI: 1.07, 3.86) or mercury (AOR=2.06; 95% CI: 1.08, 3.91) than controls. MS cases were less likely to report organic solvent exposure than controls (AOR=0.65; 95% CI: 0.28, 1.51). And statistically significant ($p<0.05$) gene-environment interactions were identified on the multiplicative scale with SNPs in five of the genes examined (*TNF*-α, *TNF*-β, *VDR*, *MBP*, and *APOE*).

At ECTRIMS/ACTRIMS 2014 meeting in Boston, several papers were reported relating to environment-gene interactions in MS. Odds of MS associated with mononucleosis greater in patients who were overweight at 20 years (Alfredsson L et al., P176). HLA-DRB1*15:01/03 modifies association of vitamin D levels and relapse risk in children with MS (Graves J et al. HT1.3). Loss of immune regulations with environmental factors that link to genetic loci.

## Conclusions

Recent GWAS studies have identified newly identified genetic risk factors, not only associated with the risk of developing MS, but the course of MS. Environmental factors such as smoking, microbiome and vitamin D levels are also studied from early onset children with

MS through pregnancy at adulthood. Future studies on interaction between the whole set of genetic risk factors and environmental factors in MS will unravel "big picture" of the mechanism of MS. Hopefully those future study results will lead to new treatments that would stop the inflammatory cascade of MS. Moreover, we would have therapeutic options to slow down degeneration phase of the disease to restore damaged CNS system.

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