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Multiple sclerosis and air pollution exposure: Mechanisms toward brain autoimmunity

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ABSTRACT

The association between neurodegenerative diseases and environmental exposures, in particular air pollution, has been noticed in the last two decades, but the importance of this environmental factor in multiple sclerosis (MS) pathogenesis has not been considered extensively. However, recent evidence suggests that major mechanisms involved in MS pathogenesis, such as inflammatory factors expression, free radicals overproduction, the blood brain barrier (BBB) breakdown, neuroinflammation, vitamin D deficiency and mitochondrial dysfunction could also occur due to exposure to air pollutants. A prospective hypothesis is suggested here in which exposure to air pollutants may initiate destructive mechanisms inducing inflammatory-oxidative cascades, reduction of immunological self-tolerance and neurodegeneration leading to brain autoimmunity.

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Introduction

According to the World Health Organization (WHO), air pollution is responsible for over 3 million deaths per year. Respiratory and cardiovascular diseases have been in the spotlight as the main causes of death due to exposure to air pollutants, but recently effects of air pollutants on the central nervous system(CNS) have emerged as a world health problem. A recent study has introduced air pollution as a main risk factor contributing to global stroke burden [1]. Additionally, it has been shown a significant association exists between ischemic stroke among young adults and particulate matter (PM) concentration in the air. Exposure to air pollution in early ages causes nasal and cognitive dysfunctions that make children susceptible to Alzheimer's disease (AD) and Parkinson's disease (PD) in adulthood. Recently, it has been shown that provocative substances, in particular PMs, are able to reach the brain [2,3]. Based on a case-control study conducted in Denmark, long-term exposure to traffic-related air pollution has a remarkable potential effect on PD risk, particularly in populations with high level of air pollution exposure [4]. Furthermore, increasing exposure to air pollutants during pregnancy and prenatal period continued to early childhood may lead to abnormalities including autism spectrum disorder (ASD), neurobehavioral effects and neurodevelopmental disorders [5–7].

Multiple sclerosis (MS) is an inflammatory, neurodegenerative and demyelinating disease that roughly affects 2.5 million people [8]. Environmental exposures, genetic predisposition and interactions between them are the keys to MS pathogenesis mystery. Exposure to air pollutants including PMs, heavy metals and airborne biological pollutants such as lipopolysaccharide (LPS) could provoke inflammatory and immune responses [9].

A strong relationship between MS relapses and air pollutants levels (PM_{10} and $SO_2 + NO_2 + NO$) was explored through a retrospective study in Finland by Oikonen and her colleagues [10]. They concluded poor air quality is able to enhance susceptibility to infections carried by PM_{10} in MS patients. In another study, they showed a significant connection between inhaled PM_{10} and

Abbreviations: AD, Alzheimer's disease; B[a]P, Benzo[a]Pyrene; BBB, blood brain barrier; CNS, central nervous system; COX-2, cyclooxygenase-2; CSF, cerebrospinal fluid; DE, diesel exhaust; DEE, diesel engine exhaust; DEP, diesel exhaust particles; EAE, Experimental Autoimmune Encephalomyelitis; EC, endothelial cell; ET-1, endothelin1; HO-1, heme oxygenase1; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MVE, monocyte chemoattractant protein1; MIF, macrophage inhibitory factor; MIP1α, macrophage inflammatory protein 1-α; MMP, matrix metalloproteinase; MS, multiple sclerosis; NF-κB, nuclear factor kappa B; NO, nitric oxide; ROS, reactive oxygen species; SOD, superoxide dismutase; TJ, tight junction; TNF-α, tumor necrosis factor alpha; PD, Parkinson's disease; PM, particulate matter; UVB, ultraviolet B; VCAM-1, vascular adhesion molecule 1.

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influenza B viral infections [11]. Interestingly, it was seen that influenza incidence has a positive correlation with MS relapses [12]. A survey performed by Gregory AC et al. disclosed that there is a potential relationship between MS prevalence and air pollution in the Georgia state, US [13]. County- level MS prevalence was displayed using Geographical information system (GIS). Results suggested that distribution of self-reported MS correlate to PM_{10} concentrations, especially in females. Recently, an Italian local research provided information that confirms the mentioned studies that there is a substantial correlation between exposure to PM_{10} and the occurrence of MS-related hospitalization [14]. There are similar studies conducted in France, Iran, and Serbia that confirm a link between exposure to air pollutants and MS relapse occurrence and hospitalization [15–17].

Hypothesis

A hypothesis is developed to organize the main mechanisms that might contribute to the increase in MS incidence and relapses in high polluted metropolitan regions.

1. Inflammation and oxidative stress compromise the Blood brain barrier (BBB) leading to neuroinflammation: Most dominant events that occur in the lung, heart, and brain in response to exposure to air pollutants are the secretion of pro-inflammatory proteins and oxidative factors compromising the barriers and leading to neuroinflammation.
2. Inflammatory- oxidative and immune attack cascades by nuclear factors and activated microglia: A compromised BBB allows passage of extrinsic compounds initializing inflammatory and immune attacks mediated by activated microglia.
3. Mitochondrial dysfunction and neurodegeneration: Exacerbation of inflammatory-oxidative attacks causes axonal damages and neuronal loss.
4. Vitamin D deficiency as an indirect effect of air pollution exposure: High levels of air pollution limits delivery of UVB to the ground level and causes a dramatic reduction in vitamin D production.
5. Autoimmunity, a possible consequence of exposure to air pollutants and changing lifestyle: Air pollution exposure could decline immunological self-tolerance by changing gut microbiome, vitamin D deficiency and producing autoantibodies.

Hypothesis evaluation

Assessing health impact of air pollutants requires high resolution data to correlate occurrence of relapses in MS patients or onset of disease in clinically isolated syndrome with variation in the levels of air pollutants.

A well designed cohort study including MS patients and healthy controls undergoing a battery of environmental history questionnaires and clinically assessed in the period of study could help better characterize the impact of environmental factors. In particular, personal monitoring of exposure to air pollutants via GPS based microenvironment trackers in MS patients serially scanned throughout the year could establish a connection between exposure to air pollutants and MS lesions in MR studies. Assessing the antibodies to Tight junctions (TJs) in the Cerebrospinal fluid (CSF) of these patients could reveal whether the alteration in air pollutants in environment could affect the BBB integrity in patients.

Pediatric patients with MS living in high polluted vs low polluted areas offer a unique research opportunity to find out whether early exposure to air pollutants could be an important factor making their immune system susceptible to develop MS symptoms in comparison to each other and in comparison to a healthy immune system.

Experimental models could reveal whether short term or long term exposure to various air pollutants, importantly Diesel exhaust particles (DEP) in exposed animals could affect the severity of Experimental Autoimmune Encephalomyelitis (EAE) and neuroinflammatory markers in study groups and the transmission pathways of these particles into the CNS could be targeted to evaluate putative neuroprotective treatments.

Discussion

Inflammation and oxidative stress compromise the BBB leading to neuroinflammation

Release of inflammatory and oxidative factors occurs in various stages of MS that lead to turning points of disease progression such as the BBB dysfunction, neuroinflammation, and neurodegeneration. Crucial role of cytokines and chemokines in MS pathogenesis should be noted as inflammatory processes occur prior to neurodegenerative and demyelinating stages. Thus, inflammation is prior to other events in MS pathogenesis.

Calderon- Garseduenas and her colleagues evaluated concentration of some inflammatory proteins in serum and CSF [18]. They selected cohorts of healthy children with high and low exposures to air pollutants. CSF analysis showed a meaningful surge in interleukin-2 (IL-2), IL-6 and macrophage inhibitory factor (MIF) levels in high air polluted areas compared to controls. IL-2 is a member of a cytokine family that plays a major role in immune system functions, tolerance and immunity via its effect on T cells differentiation [19]. Daclizumab as an anti-IL-2 receptor has been approved for MS treatment [20,21]. A survey of inflammatory biomarkers in MS patients subtypes revealed increased levels of MIF in non-progressing MS, as well as, Tumor necrosis factor alpha (TNF-α) and monocyte chemoattractant protein-1 (MCP-1), especially in PPMS. In recent years, TNF-α inhibition has been considered as a method for treatment of autoimmune diseases [22,23]. Additionally, it has recently been observed that air pollutants, especially ultra-fine particles could reach the brain tissues and activate microglia cells to release cytokines such as IL-1β, and cyclooxygenase- 2 (COX-2) contributing to in the neuroinflammation process [9,24].

In addition to cytokines, in MS patients glial cells secrete chemokines including macrophage inflammatory protein-1α (MIP-1α), and MCP-1 [25]. To explore the cellular mechanisms of neuroinflammation, rats were exposed to diesel exhaust (DE) through inhalation or intratracheal administration of the DEP [26]. The results showed substantial enhancement of whole-brain IL-6, as well as, an increase of TNF-α, IL-1β and MIP-1α in most regions of brain compared to controls. Important role of MIP-1α in Th1/Th2 lymphocyte differentiation should also be noted. Translocation of monocyte and T cells to the CNS by MIP-1α in MS patient and animal models has been shown [27,28]. Imbalanced IL-1 levels is a triggering factor of neuroinflammation linked to inflammatory autoimmune diseases including MS [29]. Low levels of DE exposure was only able to significantly increase TNF-α in the midbrain region, while notable increase occurred at higher amount of DE [30].

When production of free radicals or oxidants exceeds the neutralization capacity of the antioxidant reservoir, oxidative stress occurs. During the inflammation, released cytokines and chemokines establish communications through the nuclear factor signaling raising free radicals levels that lead to oxidative stress. This inflammatory-associated oxidative stress in activated microglia and macrophages contribute to demyelination and

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