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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.

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

neurodegenerative processes in MS pathogenesis [31]. In MS patients excess reactive oxygen species (ROS) cause activation of brain endothelial cells, tight junction gap formation, overproduction of free radicals, mitochondrial dysfunction, oligodendrocyte cell death, neural damage, and finally demyelinated axons [23]. Moreover, it is well known that inflammation surrounding demyelinating lesions results in ROS secretions [31].

Various studies have shown oxidative stress events as an inevitable outcome after exposure to air pollutants [3,32–34]. Nitric oxide (NO) is a versatile free radical which rises under expression of the inducible nitric oxide synthase (iNOS) enzyme during inflammation [35]. In demyelinating MS lesions, NO is released at high levels mediated by expression of iNOS in macrophages and reactive astrocytes [36]. Numerous studies have reported up- regulation of iNOS as major source of free radicals under exposure to traffic air pollution [3,37–40]. A significant decrease in expression of genes such as PRDX3, SOD1, and GPX3 which respectively encode antioxidant enzymes peroxiredoxin 3, superoxide dismutase 1 and glutathione peroxidase 3 in subjects exposed to high levels of air pollution versus controls was reported [32].

Along with demyelinating events, iron is released into the extracellular spaces reinforcing oxidative stress in MS lesion [41]. One of the important enzymes involved in iron metabolism is Heme Oxygenase 1 (HO-1). Exposure to proinflammatory cytokines, in particular IL-1β and TNF-α, promoted expression of glial HO-1 and mitochondrial iron deposition in astrocytes of MS patients [42]. Considerable expression of this enzyme and inflammatory factors under exposure to PM_{10} and DEE were reported by Farina [34] and van Berlo [33]. In order to evaluate the effect of short-term exposure to DEE, rats were exposed to DEE inhalation for 2 h and then the mRNA expression of iNOS, cyclooxygenase 2 (COX-2) and HO-1 in rat brain were determined [33]. Frequently interdependent expression of iNOS and COX-2 observed in MS lesions suggests these inducible enzymes are involved in inflammatory- oxidative mechanism of MS pathology [43]. There are meaningful associations between exposure to high concentrations of pollutants in ambient air and expression of COX-2 and iNOS enzymes [3,33]. Canines exposed to high concentrations of air pollutants showed brain endothelial injury could terminate to chronic inflammation and oxidative damages.

The BBB is a selectively permeable barrier arranged by brain capillary endothelial cells conjoined by TJs. The endothelial cells of the BBB play main role in prevention of provocative substances such as air pollutants, cytokines and free radicals entering the brain. Exposure of endothelium to proinflammatory cytokines (Interferon-gamma, TNF-α and IL-1β) leads to the BBB breakdown through disarranging cell-cell connections, and raises leukocyte endothelial adhesion and migration [44]. As a major feature of MS, the BBB disruption is a process with participation of proinflammatory mediators (IL-1β and TNF-α) and reactive oxygen species involved in leukocytes migration into the brain leading to axonal loss and myelin damage [44,45]. Increasing reports show that overproduction of inflammatory mediators and oxidative stress produced under prolonged and persistent air pollutants exposures mediated by cerebral endothelial cells, make a synergistic feedback that lead to BBB hyperpermeability, neuroinflammation and neurodegeneration [9,39]. This process is similar to what is seen in MS pathogenesis [46].

Up-regulation of endothelin 1 (ET-1) is observed in plasma of MS patients [47]. Under PM exposure, there is an association between increased expression of ET-1 and endothelial injuries followed by increased BBB permeability. Farina et al. proposed that enhancement of Fe^{2+} ions caused by HO-1 up-regulation under PM exposure can disturb Fenton's reaction leading to hydroxyl and nitric oxide radical production. These two factors could serve for peroxynitrite formation which is a very powerful oxidant in destruction of living cells [34]. Simultaneous increase in expression of HO-1 and iNOS can result in peroxynitrite formation. It is shown that combustion-derived nanoparticles elevate mRNA expression of HO-1, COX-2 and iNOS in the rat brain. Change in inflammatory-oxidative gene expression in rat brain disturbing the BBB function [33].

The BBB integrity disruption brings out the activated T cells and monocytes immigration leading to lesion formation in the CNS. Matrix metalloproteinases (MMPs) are enzymes that have an important role in the BBB breakdown and degradation of extracellular matrix proteins, and myelin sheaths [48]. Moreover, hyperpermeability of the BBB in the neurodegenerative disorders is linked to TJ proteins dysfunction [45]. Oppenhim and his colleagues designed an experimental study to assess whether exposure to traffic-related air pollution increases MMP-2 and MMP-9 expression and disturb function of the TJs [39]. Based on human studies, MMP-2 and MMP-9 serum and CSF levels are among important biomarker for neuroinflammation and demyelination that increase in different MS subtypes [29,49]. Mice were exposed to mixed vehicle exhaust and filtered air for 6 hr/day and 30 days. Compared to controls, exposed mice showed increased MMP-2 and MMP-9 activity and elevated level of ROS resulting in increased BBB permeability. In addition, increased level of neuroinflammation markers was indicated in cerebral microvasculature of exposed mice.

According to the report presented by Felts and his colleagues, injection of bacterial-derived LPS into the spinal cord is able to cause inflammation and oxidative stress through substantial expression of IL-1β and iNOS in microglia cells and induce primary demyelination. Interestingly, a surge in intercellular adhesion molecule 1 (ICAM-1) expression and lymphocyte infiltration were observed in the lesions [50]. After adhesion to activated brain endothelial cells, immune cells release ROS leading to TJ disruption and migrate to the other side of the endothelium [23]. It should be noted that in a healthy brain, adhesion molecules that are essential for leukocyte migration are expressed by the endothelial cells in low levels [51]. Abnormal expression of adhesion molecules such as ICAM-1 in endothelial cells could be stimulated by LPS, TNF-α and IL-1β facilitating the BBB breakdown [52].

Brain tissues of deceased people from cities with high and low levels of air pollution were examined. Up-regulation of COX-2 and IL-1β in different brain regions, TJs disruption, nuclear factor activation in brain endothelial cells, increased expression of vascular cell adhesion molecule 1 (VCAM-1) and ICAM-1 in endothelial cells and finally altered BBB were observed in high polluted city samples compared to controls [9]. The presence of PM in brain regions; for example the olfactory bulb, and translocation of ultrafine particles from the lung to perivascular macrophage-like cells in frontal capillaries imply that the BBB has been disrupted.

As mentioned earlier, up-regulation of adhesion molecules including ICAM-1 stimulated through LPS, IL-1β, and TNF- α leads to leukocyte adhesion to the endothelial cell and then migration of T cells into the brain. This process causes a dramatic increase in immune attacks and compromises the BBB. For the first time, by an in vivo study was shown that interaction of the lymphocyte with ICAM-1 activates nuclear factor kappa B (NF-κB) which resulted in dysregulation of expression and secretion of brain endothelial P-glycoprotein in MS animal model [53]. It is revealed that expression of P-glycoprotein as a CNS transporter is altered under exposure to mixed vehicle exhaust [39]. Harts and his colleagues demonstrated that DEP could target the brain capillary endothelium via a change in p-glycoprotein expression and transport activity. Functional analysis of isolated brain capillary in rats exposed to DEP indicated that up-regulation of p-glycoprotein in brain capillaries is signaled by nuclear factors, oxidative stress, and proinflammatory cytokines production. Analysis of results

confirmed the primary source of generated ROS is brain capillaries [40]. Generation of ROS in brain capillaries has a considerable potential to damage epithelial and endothelial cell junction components leading to the BBB malfunction and entry of extrinsic agents into the brain.

Supporting above evidence, outcomes from a pilot study located in a high polluted city showed there is a potential association between air pollution exposure and brain alterations such as significant up-regulation of inflammatory genes, the BBB disruption, brain deposition of ultrafine particles, and neuroinflammation [24]. In this study, almost three-fifths of children and dogs tested by brain magnetic resonance imaging (MRI) represented prefrontal white matter hyperintense (WMH) lesions and enlargement of Virchow–Robin spaces (VRS).

Inflammatory- oxidative and immune attack cascades by nuclear factors and activated microglia

Microglial and astrocyte activation is one of the main players in CNS demyelination [54,55]. In MS patients, activated microglia mediate free radical production, oligodendrocyte-myelin damage, and finally demyelination [56]. The shapes of activated microglial cells are amoeboid and ramified. Polarization of microglia toward one of them, determine type of function, inflammatory or *anti*-inflammatory. When microglia cells are activated by LPS, PM, cytokines, and chemokines, they are polarized toward the amoeboid shape and increase expression of TNF-α, IL-1β, and IL-6; as well as, iNOS and COX-2 via different signaling processes particularly via NF-κB leading to inflammation and oxidative stress [55].

Expression of numerous genes involved in oxidative stress, inflammation, and cell differentiation are regulated by transcription factors, especially NF-κB signaling [57]. Functions of NF-κB in CNS are more than other organs. It has the major role in response to stimuli such as free radicals and inflammatory substances; as well as, its regulatory role in immune response related to T and B cells. Hence, disturbance in NF-κB activities is linked to autoimmune diseases including MS [58].

Experimental research on healthy dogs exposed to high concentration of air pollutants exhibited expression of neural NF- κB, tremendous expression of iNOS in astrocytes, microglia and endothelial cells, the BBB dysfunction, apoptotic glial white matter cells and degeneration of cortical neurons [38]. For the first time Dutta et al. showed Benzo[a]Pyrene (B[a]p), a polycyclic aromatic hydrocarbon, induce neuroinflammation by initiation of inflammatory cascades in CNS [37]. Different doses of B[α]p were injected to mice intraperitoneally and then glial cells were extracted from them. Besides, microglial cells were treated with B[α]p. Morphological signs of microglia activation were observable even 48 h after incubation. This microglial activation led to increasing of intracellular ROS significantly. Upon treatment of microglia cells, release of NO increased dramatically because of elevated iNOS expression within microglia. Moreover, microglial activation gives rise to bystander neuronal death by up-regulation of inflammatory proteins such as TNF-α and IL-6. As mentioned above, it may be inferred that inflammation and oxidative attacks polarize microglia cells to amoeboid shape and then activated microglia cells stimulate free radical overproduction and inflammatory cascades. Formation of a cycle consisting of air pollutants, activated microglia, and nuclear factors produces reinforcing feedback that expands neuroinflammation, keeps the BBB compromised and intensifies expression of inflammatory and oxidative factors. All these events are going to lead to neurodegeneration and CNS autoimmunity [55,59].

In another experimental research, Li and his colleagues showed LPS activates microglia cells followed by overexpression of iNOS [22]. Simultaneous up-regulation of NADPH oxidase to produce peroxynitrite, a powerful oxidant that contributes to oligodendrocytes death in white matter disorders such as MS. In studies that have investigated effects of exposure to outdoor air pollution, in vivo and in vitro, activation of microglia and transcription factors has been reported [3,9,37,38,40]. Activated microglia and nuclear factors are responsible for initiation of signaling pathways that have a critical role in inflammatory cascades, immune responses and finally neuroinflammation.

In Experimental Autoimmune Encephalomyelitis (EAE) model, MIF is a key player in the production of iNOS, TNF-α, IL-6, and IL-1β as well as microglial activation. In addition, it is associated with the clinical exacerbation and relapsing in MS patients [60]. Increased level of this neuroimmune mediator in CSF and serum of children exposed to heavy air pollution could be regarded as a link between neuroinflammation and worsening of immune responses resulting in autoimmunity [18,60,61]. Formation of pathways from microglia activation and iNOS (oxidative stress inducer) to the inflammatory proteins expression accompanied with MIF assistance can establish inflammatory and oxidative cascades leading to dysregulated neural immune responses.

Mitochondrial dysfunction and neurodegeneration

Neurodegeneration is the umbrella term for the process of the neuronal loss mainly, functional and structural loss of neurons, axonal damages and neuronal death [62]. It has been indicated a neurodegenerative process mediated by mitochondrial dysfunction plays a considerable role in early stages of MS pathogenesis [63]. Oxidative stress is the central core of all neurodegenerative diseases. Under inflammatory-oxidative circumstances, microglia cells produce quite a lot of reactive oxygen and nitrogen species including nitric oxide, hydroxyl and peroxynitrite radicals. Such free radicals overproduction may disrupt neuronal/axonal mitochondrial function and structure which terminate to hypoxia, decreased ATP level, more ROS secretion and ultimately neuronal injuries [23,62]. It has been shown that neural tissue loss mediated by activated microglia and mitochondrial dysfunction occurs under exposure to air pollutants particularly, PMs [64–66].

Increased level of NO with destructive effects on mitochondria has been seen in reactive MS lesions [67]. It should be pointed that in micro-molar concentrations of NO oxygen can be replaced by NO and then inhibits the enzyme cytochrome C oxidase. After that, the respiratory chain interrupts and lead to oxygen deficiency in brain tissues. The required NO for this reaction may be supplied via iNOS intracellular overexpression. Although reversibility of the inhibited cytochrome C oxidase may depend on exposure time and concentration of NO, under hypoxia condition nitric oxide molecules inhibit this enzyme irreversibility [68]. As previously mentioned, excess NO reacts with superoxide produced by NADPH oxidase and microglia to form peroxynitrite radicals that can breakdown to high reactive species such as hydroxyl and nitrogen dioxide radicals increasing oxidative stress and cell toxicity. In many studies, up-regulation of glial and neural iNOS and extra production of NO under exposure to one or more air pollutants have been reported [3,38–40]. Together, oxidative stress caused by air pollutants contribute to mitochondrial dysfunction and oxidative metabolism disruption in damaged axons resulting in hypoxia, decreased ATP production and neural loss which have been seen in MS patients [8,62]. In addition, hypoxia in inflamed tissues is able to disrupt TJs and damage to the integrity of the BBB [69].

Vitamin D deficiency as an indirect effect of air pollution

High circulating vitamin D had significantly lowered risk of MS in a case control study [70]. RRMS patients had lower vitamin D levels during relapses compared with patients in remission.

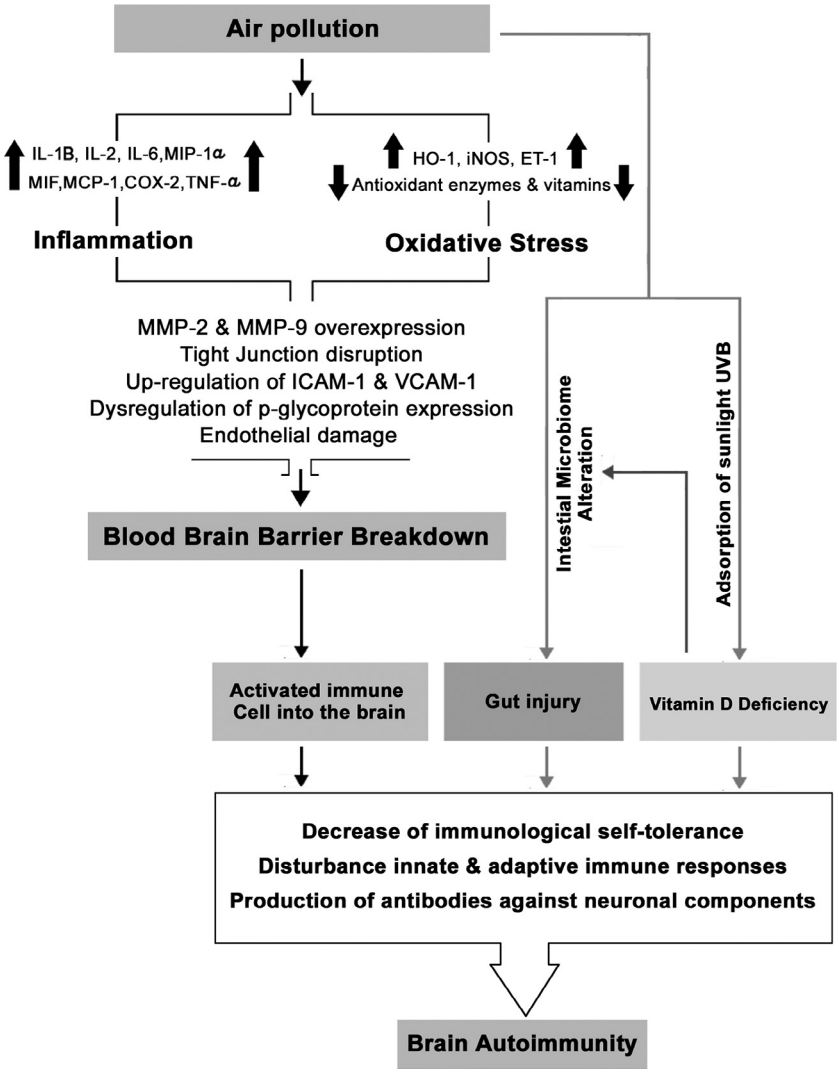

Fig. 1. Air pollution exposure and mechanisms in multiple sclerosis pathogenesis: Inflammation and oxidative stress lead to blood brain barrier breakdown, immune attack cascades by nuclear factors and activated microglia, mitochondrial dysfunction and neurodegeneration, and vitamin D deficiency could culminate in brain autoimmunity. (COX-2, cyclooxygenase2; ET-1, endothelin1; HO-1, heme oxygenase1; ICAM-1, intercellular adhesion molecule1; IL, interleukin; iNOS, inducible nitric oxide synthase; MCP-1, monocyte chemoattractant protein1; MIF, macrophage inhibitory factor; MIP1α, macrophage inflammatory protein1-α; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa B; SOD, superoxide dismutase; TNF-α, tumor necrosis factor alpha; UVB, ultraviolet B, VCAM-1, vascular adhesion molecule1).

Vitamin D prevents autoimmunity through different mechanisms: 1,25 $(OH)_2$ Vit D inhibited CD4+ T cell proliferation, and increased vitamin D receptor expression in CD4+ T cells. IL-10 producing T cells were increased in presence of 1, 25 $(OH)_2$ Vit D and IL-6 and IL-17 producing cells were decreased in RRMS patients. Interestingly, CD4 + CD25 + FoxP3+ regulatory T cells, able to arrest the development of autoimmune responses, were significantly increased when PBMCs from RRMS patients were cultured in the presence of 1,25 (OH)2 Vitamin [71].

More than ninety percent of the required vitamin D in human body are provided through sunlight exposure [72]. Air pollution contributes to modulation of immune responses through vitamin D. Absorbing and scattering solar UVB radiation by air pollutants reduce the effectiveness of sun exposure in vitamin D production [73]. Hence, air pollution level has a determining role in the development of vitamin D deficiency. Thus, hypovitaminosis D is proposed as an indirect effect of air pollution in high polluted regions with plenty of sunlight. A recent cross-sectional study conducted in Belgium showed exposure to air pollution mainly the tropospheric ozone increases prevalence of D hypovitaminosis among women [74]. A similar study performed in Iran revealed there is a significant association between vitamin D deficiency in women and living in a polluted area [75]. The high prevalence of vitamin D deficiency in megacities' children confirms air pollution as a risk factor in the pathogenesis of vitamin D hypovitaminosis [76,77].

HLA-DRB1*1501 allele has been identified as the strongest genetic risk factor in MS [78]. Functional characterization of genetic susceptibility variants that interact with environmental factors to determine the MS risk is still underway, vitamin D as an environmental risk factor in MS directly interacts with HLA-DRB1*1501 via vitamin D response element(VDRE) in HLA-DRB1 promoter region [79]. Although major histocompatibility complex (MHC) region on chromosome 6 has been identified as major MS risk factor for many years, there are now 110 established MS risk variants in 103 discrete loci outside of the MHC identified through fine mapping via Immunochip genotyping arrays [80]. Further functional studies could unravel the role of susceptibility variants that could interact with air pollutants as possible environmental risk factor in MS determining high risk population who might develop MS symptoms while exposed to air pollutants.

Autoimmunity, a possible consequence of exposure to air pollutants and changing lifestyle

Oikonen et al. observed that peak amounts of PM_{10} have a significant relationship with MS relapses in south western Finland, a fourfold odds ratio of MS relapses was shown when PM_{10} was in highest quartile [10]. A similar study in Italy revealed increased admission between 0–7 days after exposure to high levels of PM_{10} [14]. A recent study in Strasbourg, France included 251 patients with 1136 relapses during 2000–2009 and found significant difference in exposure to PM_{10} among MS patients and controls during 3 days before occurrence of relapse [15]. An epidemiological study showed a connection between influenza infections and inhaled PM_{10} [11]. In addition, second correlation was discovered between influenza incidence and MS onset [12]. According to a well-known theory related to chronic and latent infections, MS pathogenesis may be related to autoantibodies mediated by inhaled PMs through molecular mimicry. The molecular mimicry is one of the accepted hypotheses in MS etiology resulting in decreased immunological tolerance which sets immune attacks to myelin and oligodendrocyte [81].

Exposure to air pollutants has a great potential to trigger antibody production against cerebrospinal proteins. Findings suggest chronic exposure to air pollutants has a significant correlation with released antibodies against neural proteins, especially myelin basic protein (MBP), S-100 protein, and myelin oligodendrocyte glycoprotein (MOG) [82]. Serum levels of antibodies against outdoor air pollutants including Benzene, Formaldehyde, Bisphenol A and heavy metals were substantially higher than controls. Importantly, the presence of S-100 protein, MBP and MOG antibodies is indicated as biomarkers for MS [29]. Besides, CSF analysis showed a strong correlation between neural antibodies and concentration of Benzene, LPS and heavy metals including Cr, Co, and Pb [82].

It is proposed that a large number of autoimmune diseases occur because of changing lifestyle through industrialization and urbanization development [83]. Environmental toxicants, most importantly air pollutants, are among these widespread changes. Gut microbiome alteration plays an impressive role in autoimmune diseases through modulation of immune responses [84]. Recently, it has been discovered exposure to air pollutants containing heavy metals such as mercury and cadmium is able to modulate gastrointestinal microbiome and result in systemic inflammation and immune activation [85]. Gut microbiome alteration can also be due to vitamin D deficiency leading to autoimmunity [86]. The high serum level of Vitamin D (above 40 ng/ml) in MS patients is associated with increased abundance of a bacterial family (Ruminococcaceae) which produces *anti*-inflammatory fatty acids. It should be noted that low level of this species has been related to Crohn's disease. Such effects may increase inflammation leading to increased MS symptoms. In fact, the vitamin regulates gut flora composition as low level of vitamin D induces dysbiosis. A leaky gut caused by unsuitable diet or air pollutants lead to systemic inflammation and immune activation could participate in autoimmune diseases via autoantibodies production. Therefore, air pollution through two interconnected mechanisms contributes and reinforces the conversion of gut flora; firstly by vitamin D deficiency and secondly by gut leakage and release of autoantibodies. In an overview, Fig. 1 shows all major interactions which may lead to the brain autoimmunity under air pollution exposure.

Conclusion

Chronic exposure to high levels of air pollution raises the pro-inflammatory factors secretion and develops ROS through circulatory system upward brain cells. CNS inflammation, breakdown of the BBB integrity and significant increase in autoantibodies in the brain, are most important events which occur under exposure to air pollutants particularly by LPS-PM and $PM_{2.5}$ leading to neuroinflammation and neurodegeneration.

This hypothesis suggests that pathogenesis of MS has considerable similarities with adverse inflammatory effects contributed to exposure to air pollutants. As depicted in Fig. 1, air pollution exposure is able to create a self- sustaining network of inflammatory, oxidative and immunological feedback that can contribute to brain autoimmunity. Consequently, industrial and traffic air pollutants may be one of the main clues of increasing MS prevalence in polluted megacities such as Isfahan and Tehran in last 2 decades. Therefore, it is possible to take into account air pollutants exposure as one of the rational causes in the growing MS rate in high air polluted areas.

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