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Review Article

Neurological complications related to COVID-19 infections following exposure to airborne aerosol particles

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Abstract

Some of the recent researches show that air pollutants such as particulate matter (PM), including fine particles (PM<2.5μm, PM2.5) and very fine particles (PM <0.1μm, PM 0.1) can reach the brain and affect CNS health. Neurological complications with Coronavirus Disease 2019 (COVID-19) have been observed. The aim of this review the relationship between air pollutants exposure and COVID-19 was focused on the role of airborne aerosol particles in the prevalence of the disease, as well as the neurological effects of COVID-19. It is not yet clear how the virus is transmitted from one sick person to another and why it is so transmissible. Viruses can be probably transmitted through speech and exhalation aerosols. Findings show that SARS-CoV-2 aerosol transmission is possible. Spike (S) proteins of SARS-CoV-2 determine tissue tropism using an angiotensin-converting enzyme receptor type2 (ACE-2) to bind to the cells. ACE-2 receptor is found in the tissues of the nervous system. Neurological disorders that occur with COVID-19 can have many pathophysiological backgrounds. Some are the result of a direct viral attack on tissues of the nervous system, others appear to be an autoimmune process post-viral, and still others appear to be the result of systemic and metabolic complications associated with critical illness.

Keywords: covid-19 infections; aerosol transmission; airborne aerosol particles; neurological complications; air pollution exposure

Abbreviations

Ang I	Angiotensin I
Ang II	Angiotensin II
Ang II (1-7)	Angiotensin-(1-7)
ARDS	Acute Respiratory Distress Syndrome
ACE	Angiotensin-Converting Enzyme
ACE2	Angiotensin-Converting Enzyme 2
AT1R	Angiotensin II type 1 receptor
ANE	Acute Necrotizing Encephalopathy
BBB	Blood–Brain Barrier
OB	Olfactory Bulb
HI	Hippocampus
CO	Carbon Monoxide
CNS	Central Nervous System

COVID-19 Coronavirus Disease 2019

ERK Extracellular Signal-Regulated Kinase

IL Interleukin

NO2 Nitrogen Dioxide

O3 Ozone

PM Particulate Matter

PM0.1 Particulate Matter < 0.1 µm (ultrafine particles)

PM2.5 Particulate Matter < 2.5 µm (fine particles)

PM10 Particulate Matter with a diameter between 2.5 µm and 10 µm (coarse particles)

RBD Receptor Binding Domain

ROS Reactive Oxygen Species

RAS Renin Angiotensin System

SO2 Sulfur Dioxide

STAT3 Signal Transducer and Activator of Transcription 3

SARS Severe Acute Respiratory Syndrome

SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus 2

TNFα Tumor Necrosis Factor alpha

INFγ Interferon-gamma

UFPs Ultra-Fine Particles

US United States

HCOV Human Coronavirus

Introduction

The mechanisms by which air pollutants exposure, such as ultrafine particulate matters (UFPs; <100 nm), can affect respiratory health and includes pulmonary inflammation, which can lung function reduction through contracting bronchi or altering the immune system pulmonary [1, 2]. In general, ambient particles include elemental and organic carbon, inorganic components (trace metals, nitrates, sulfates, chloride, and ammonium), biological components (pollens, bacteria, and spores), volatile and semi-disintegrating organic compounds [3]. Furthermore, when the ambient particles are mixed with atmospheric gases (carbon monoxide, sulfur, ozone, and nitric oxides), they can form airborne particles. Environmental particles are commonly characterized by aerodynamic properties and their size and defined as PM2.5 and PM10 with diameters of less than 2.5 and 10µm: PM with an aerodynamic diameter of 2.5 to 10µm (PM10), PM smaller than 2.5µm (PM2.5) and very small PM less than 0.1µm or UFPs. These particles are acceptable fractions from different sources such as agricultural dust, wood combustion, road, vehicles emission, tire wear propagation, construction, mining operations, and demolition work [4, 5].

In parallel, exposure to UFPs could significantly exacerbate inflammation by cellular proliferation and reorganization of the extracellular matrix [6], as well as weakening the pulmonary immune response [7]. This mechanism has been described by several toxicological studies [7, 8] and a lot of epidemiological evidence corroborates the role of exposure to chronic and acute air pollutants in the admission of respiratory hospitals, such as exacerbation of asthma [9] or chronic obstructive pulmonary disease [10].

Furthermore, several studies reported that air pollution exposure exacerbates the intensity of various respiratory diseases [11], for example influenza infection [12] and severe acute respiratory syndrome (SARS) or another coronavirus [13]. One study in the US indicates that exposure to PM2.5 and ozone was dangerous and increased the risk of SARS among older adults [14]. Based on this presupposition, it is possible that the air pollution exposure will alter the intensity of the COVID-19 symptoms or help explain the differential-spatial patterns of disease prevalence. Recent surveys have reported that people with severe COVID-19 may already have the respiratory disease [15-22]. Recent studies on viral respiratory disease (such as influenza) have shown that a viable virus can be emitted from infected peoples by speaking even breathing, without sneezing or coughing [23, 24]. Normal and ordinary speech converts significant amounts of respiratory particles into airborne aerosols. Experimental research has shown that vocalization emits up more aerosols than breathing [25], also, a recent study indicated the louder one speech, the more aerosols are produced [26]. COVID-19 is a severe respiratory infection, and recent studies clearly identified the SARS-CoV-2 presence in a tract of the respiratory system [27]. Therefore, particles derived from breath and speech may contain viruses. These particles may be due in part to the mechanism of "liquid film bursting" in alveoli in the pulmonary, and or through the vibration of the vocal cords during a speech [28]. The findings suggest that particles and aerosols in the air reach the brain and affect CNS health, with changes in the blood-brain barrier (BBB) or leakage and transmission along the olfactory nerve to the olfactory bulb (OB) and active Microglia are the main components [29, 30].

The relationship between air pollution exposure and COVID-19

Based on the previous studies, air pollutants exposure is closely related to respiratory infection due to other microorganisms [8, 11]. Also, it was shown that exposure to a high concentration of PM2.5 was associated with more acute lower respiratory infections [42]. A significant association between exposure to urban air PM and hospitalizations due to respiratory disease was reported using a model of distributed lag nonlinear [43]. In Thailand, time series analysis performed found that PM10, SO_2, CO, O_3 and NO_2 were significantly related to an increased risk of admission to respiratory hospitals [46]. Another review found that exposure to NO_2, SO_2, and CO could increase the risk of respiratory diseases and was harmful to health [47]. Another study showed that there was a statistically significant link between exposure to a high level of air pollutants such as PM10, PM2.5, NO_2, O_3, CO, and COVID-19 infection [22, 33].

The COVID-19 is caused by SARS-CoV-2 [31-33], and it was first observed in December 2019 [34, 35]. In the following months, it rapidly spreads to all of China and gradually became a pandemic public health problem in the whole world [32, 36, 37]. Various studies have demonstrated that the risk of COVID-19 infection could increase following human-to-human contacts [36, 38, 39]. Thus, the mobility of the population has a remarkable effect on the COVID- 19 pandemic [40]. Previous findings have shown that exposure to urban air pollutants by carrying microorganisms is a risk factor for respiratory infections to make the pathogens invasive to the humans and affect the body's immunity to more expose people to pathogens [41-44]. Because COVID-19 is a severe respiratory disease and the SARS-CoV-2 can survive for hours in an aerosol. The impact of exposure to air pollution needed a careful survey [45], thus, the investigation of the effect the air pollution exposure on the COVID-19 infection is very interesting.

The concentration of PM2.5 as the main stem of viral susceptibility

Chronic exposure to air pollutants such as PM2.5, SO2, and NO2causes reduce lung function, respiratory disease, and cardiovascular disease [48-50]. In addition to causing a persistent inflammatory reaction, air pollutants have been shown to increase the risk of viruses targeting the respiratory tract, even in relatively young people [16, 17]. PM2.5 penetrates into peripheral lung air spaces [51] and can through interaction with the renin-angiotensin system (RAS) facilitate the viral infection. The pulmonary RAS include the two axes involved in the local inflammatory responses with the opposite functions [52]: the ACE /AngII /AT1R axis that is involved in the release of proinflammatory cytokines (TNF-a and IL-6). The ACE-2/Ang1-7/Mas axis that culminates in the Mas activation concludes that affects STAT3 and ERK and produces an anti-inflammatory effect. The angiotensin-converting enzyme2 (ACE2) protects against the RAS induced damage through two processes: 1) degradation of AngI and AngII to limit the substrate availability in adverse the receptor axis of ACE /AngII /AT1; 2) production of Ang1-7 to increase the capability of the substrate in ACE-2 /Ang1-7 /Mas receiver axis [52]. The ACE-2 knockout mice after the PM2.5 exposure are more prone to lung damage and reduced pulmonary repair compared to controls. This indicates an important role for the ACE-2 in protecting the lungs against air pollutants [53]. Chronic exposure to PM2.5 leads to upregulation of the pulmonary ACE expression and activity in mice that can be the protective response to the chronic harmful injury [53, 54]. Also, despite having normal function and structure of the lung, ACE-2 knockout mice compared with the control mice of wild-type, showed very intensive pathology of the acute respiratory distress syndrome (ARDS) [53, 55]. Coronavirus protein's spike facilitates the viral entry into the target cells by engaging the ACE-2 receptors [56]. ACE-2 is, predominantly expressed at the level of the alveolar, and explains viral tropism for the lower airways. In fact, by the interaction between the S1 subunit receptor-binding domain (RBD) in viral spike glycoproteins with ecto ACE-2 domain, binding and entry are facilitated of the SARS-CoV and the SARS-CoV-2 into the human cells [57].

Infection and challenge of SARS-CoV with recombinant SARS-Spike protein significantly reduces ACE-2expression in the lungs and in the cell culture and led to more severe lung damage [58]. Reduction of viral ACE-2 emerges to be very important in mediating lung damage [58, 59]. We postulate that overexpression of ACE-2 in patients who are chronically exposed to the high concentration of PM2.5 can facilitate the viral penetration, resulting in a decrease in ACE-2 leading to more intense forms of the disorder. This may explain the low incidence of severe pneumonia in the children, most of whom are asymptomatic. Limitations in PM2.5 exposure owing to young age in children may excuse them from overexpression of the ACE-2 receptor. Out of all infected patients in China, less than 1% were under 10 years old children [60] that developed milder disease [61]. Therefore, chronic upregulation of the ACE-2 in the PM 2.5 dose-dependent manner can explain a wide variety of clinical manifestations from asymptomatic patients to patients with severe, moderate, or mild diseases [61]. According to findings, the average viral load is 60 times higher in the SARS-CoV2 severe cases than in the mild cases [62].

While the Covid-19 causes only mild symptoms in most patients, in rare cases it can lead to an extreme-inflammatory response leading to ARDS and death.

In addition to the clear overlap between the Covid-19-induced ARDS symptoms and prolonged air pollution exposure, there is evidence of an association between Covid-19 cases and ozone and nitrogen oxide concentrations[15]. Another study in northern Italy found that air pollutant concentrations may play a role in increasing Covid-19 mortality in that region [16]. Similar evidence in Italy suggests that PM may actually carry the virus and thus directly contribute to its spread [63]. In the Netherlands also, preliminary analysis evidenced a link between the PM2.5 concentrations and Covid-19 cases [64]. Results of the study of the relationship between the Covid-19 mortality rate and long-term exposure to the high concentration of PM2.5 in US cities show that an increase of 1μg / m3 in PM2.5 concentration was associated with the 8% increase in the death rate of Covid-19 [18].

Air pollution exposure and neurological complications of COVID-19

A body of evidence that supports the involvement of CNS in path physiology of the COVID-19 is increasing. Though COVID-19 mainly affects the respiratory and cardiovascular systems, the recent reports suggest that it can cause certain neurological symptoms including hypoglycemia, dizziness, headache, encephalitis, encephalopathy, acute cerebrovascular events, a disorder of consciousness, skeletal muscle injury, and poly Neuritis that can the even precede common features such as cough and fever [65]. Furthermore, the recovered COVID-19 patients without specific neurological manifestations during the acute stage also showed brain damages even three months after discharge [66]. Mechanically, have been proposed several pathways in which SARS-CoV-2 led to neurological complications such as direct damage to specific receptors and neurons, secondary hypoxia, cytokine-related damage, and reversal travel along fibers of the nerve [67]. In any case, the exact mechanisms of COVID-19 neurological manifestations are largely unattainable. Generally, neurological dysfunction can be a result of systemic disease, direct viral injury, and /or systemic inflammation [68]. The virus can interact with the brainstem pathways, thus in addition to direct lung damage, leading to indirect respiratory dysfunction. The coronavirus uses the ACE2 receptor to enter cells and circulate. Because also these receptors are found in the brain glial cells and the spinal neurons, they can attach to, multiply and damage the neuronal tissue [65].

Some studies indicate that the SARS-CoV-2, which resembles the UFPs, can reach a brain through an olfactory nerve and OB [30, 69]. Viral binding to BBB endothelial cells through ACE2 expression further disrupts the BBB and facilitates viral entry into CNS. Pulmonary viral invasion causes systemic inflammation (through increased levels of IL-6, IL-12, IL-15, and TNFα), leading to a CNS pro-inflammatory state through glial cell activation [30, 67]. Local and systemic effects of the lung alveolar together cause severe hypoxia and ultimately lead to cerebrovascular dysfunction [67]. Recently, the examining relationship between coronavirus mortality and prolonged NO_2 exposure showed that air pollution exposure may be a major contributor to COVID-19-related mortality [15, 22].

The SARS-CoV-2 known pathophysiology and other Coronaviruses provide clues as to the possible mechanisms of CNS damage. Now it has been shown that SARS-CoV-2, like other human Coronaviruses (HCoV) of which the SARS-CoV-2 virus group is a member, can attack the CNS. The SARS-CoV-2 attack is thought to require both cell surface receptors to viral spike protein binding and S protein priming by cell proteases. In particular, SARS-CoV-2 uses ACE2 as the input receptor and the cell protease of TMPRSS2 for the S protein primer [70]. Cross surveys on ACE2 and the TMPRSS2-positive cells on human tissue found these proteins the expression in the nasal goblet and the ciliated epithelial cells and also oligodendrocytes [71]. Co-expression of ACE2/TMPRSS2 in

oligodendrocytes can be one method of CNS proliferation or infiltration. During the SARS-CoV pandemic, encephalitis acute cases were reported with the virus detected in the patient CSF [72, 73]. Some pathological studies reported that infectious virus and viral RNA were identified in the brain tissue. In post-mortem four SARS-CoV patients examination and four individuals control, found SARS-CoV RNA and antigen in the cerebellum of people infected with SARS-CoV [74]. Other Coronaviruses have already been found in autopsy studies in the brain:

OC43 and HCoV 229E strains were identified in 44 of the 90 brain donors determined by RT-PCR [75]. OC43 prevalence in patients with multiple sclerosis (MS) was significantly higher than in the control group. Besides, another study showed MCP-1 chemokine mRNA increase in the astrocyte cell lines due to infection of HCoV-OC43[77]. Therefore, these results indicate that HCV infection can exacerbate the neuropathology of MS, raising the possibility that the coronavirus infection can interact with preexisting neuropathology or coexist, leading to neurological or chronic complications create. Coronaviruses can invade the CNS through a transneuronal or hematopoietic pathway. The early SARS-CoV-2neuroinvasion may be via the OB [78]. Air pollution nanoparticles transport from nasal epithelium to olfactory nerve and then hippocampus (HI) has been shown in mice models [29, 30]. HCoV transport also from nasal epithelium to olfactory nerve and then CNS has been shown in rat models. Only three days after HCoV-OC4 intranasal inoculation, the transgenic mice had cells containing specific viral antigens in OB. During the seven days post inoculation, at the same time as fatal clinical encephalitis, the virus spread throughout the whole brain. In mice, like HCoV-OC43, following experimental nasal inoculation, SARS-CoV has been found in CNS. Within over 1-2 weeks after infection, and approximately eight-fold increase in density of SARS-CoV-positive cells was observed in the CNS, mainly accumulated in the HI [78]. Clinically SARS-CoV is associated with encephalitis cases, viral particles, and ischemic changes in the neurons and genome sequencing has been detected in human autopsy in the brain [79].

Although the genomic identities of SARS-CoV and SARS-CoV-2 are up to 82% similar, SARS-CoV-2 have unique genetic traits, particularly encoding proteins that can contribute to both virus replication and pathogenicity [80]. The significance and implications of genetic differences are still unclear. Coronaviruses may be cross into CNS through the BBB that is compromised by inflammatory mediators, endotheliitis or endothelins injury, transmigration of virus-carrying macrophages, or direct endothelial cells infection themselves [71, 75, 81].

SARS-CoV, the SARS responsible virus, after deployment in the CNS, has been shown that to be rapidly capable of the transneuronal proliferation and infected neurons death in models of transgenic mice that express human ACE2 receptors [82]. Some of the infected mice with HCoV-OC43, the human coronavirus causing the common cold, develop a neurological infection and acute encephalitis or may survive the acute infection and behavioral changes of developing chronic encephalitis and OC43 virus persistence indicate that neurons were affected [83]. Infection of cortical neurons and hippocampal by HCOV-OC43 in the tissue culture have shown that the death of cells may occur due to apoptosis of the infected, neighboring and non-infected cells [83]. Previous findings have shown that TNF-α, a known stimulant for apoptosis, is released by the infected cells and can be involved in uninfected cells apoptosis and in microglia infiltration and activation [84]. Both SARS-CoV-2 and the SARS-CoV enter the host cells via ACE2 receptors, but the phylogenetic data and complex receptor analysis at the atomic level suggest that coronavirus can recognize the human ACE2 with greater efficiency [85, 86].

In one study that introduced soluble human SARS-CoV-2 and ACE2 (hrsACE2) at the clinical-grade in the engineered human tissue, the hrsACE2 was capable of effectively inhibiting the virus and preventing it from attaching to cells [87]. ACE2, which is high levels expressed in the various tissues including brain endothelial cells, type 2 alveolar cells, glial cells, and neurons [88-90], the renin-angiotensin system regulates by opposing ACE signaling via the production of vasodilator peptide angiotensin [91-93]. Has been shown SARS-CoV to reduce the ACE2 levels in mice lungs without detectable altering in the ACE expression [58]. By reducing ACE2 regulation expression, the SARS-CoV-2 can upset the ACE/ACE2 cerebrovascular control delicate balance, which may lead to excessive vasoconstriction, unopposed ACE signal, or impaired cerebral auto regulation. It has previously been shown that SARS-CoV infection with high levels of cytokines, including TNFα, IL-6, IL12, IL-1β, and INFγ, is a phenomenon known as the "cytokine storm" [91, 94], these pro-inflammatory cytokines high levels are associated with poor outcomes. The SARS-CoV-2 has such pathogenicity because the severity of COVID-19 is now associated with increased levels of TNFα, INFγ, IL-17, IL-10, IL-8, IL-7, IL-6, IL-2, IL-1β, INFγ-inducible protein-10, MCP1, and G-CSF [91, 95, 96]. Elevated IL-6 and ferritin, hyper inflammation markers, have previously been associated with mortality in the COVID-19 [91, 97]. Cytokine storms can contribute to neurotoxicity and acute lung injury; the mice infected with the influenza A virus showed a significant increase in cytokines IL-1β, IL-6, and TNF-α with excessive vascular permeability in the lungs and also brain within the 6 days of the inoculation [98]. The BBB integrity can be disrupted by immune-mediated toxicity and cytokine-induced damage in absence of the direct viral spread and or attack. Findings suggest that ANE, for example, maybe caused by cytokine toxicity [99]. Also, cytokines can be directly neurotoxic, mediating or even inhibiting CNS cell injury either acting alone or synergistically [100]. The methods in which observed highly activated signaling of cytokine in infection of SARS-CoV-2 may affect neuronal outcome via altering neuro-inflammatory pathways are not known [101].

Conclusion

Scientific studies on exposure [102] can help transmit the virus *via* aerosol, how to use personal protective equipment in personal exposure, source of entry into the receptor pathways, the survival of the virus at different levels, in various environments conditions and meteorological including temperature, ultraviolet radiation, humidity [103, 104]. Extreme heat and or the arrival of the cold season and decreasing air temperature and the occurrence of temperature inversion, especially in crowded cities, can interfere with the dispersion of air pollutants on the ground level and increase the concentration of pollutants and the health damage.

Considering the additional risk that some communities may face withCOVID-19 and the extra burden that they face during severe weather events, also the interplay between COVID-19 prevention measures and coping strategies against the severe reduction of air temperature in cold seasons and or extreme heat (for example, restrictions on service centers and shops, respect for social distance, wearing a mask despite the occurrence of respiratory distress, the occurrence of temperature inversion in winter and increasing concentrations of air pollutants, and traffic restrictions in cities, …), epidemic preparedness strategies are essential for the climate adaptation. In these time-sensitive pandemics, to help inform the targeted interventions and reduce disease prevalence

while minimizing socio-economic inequalities and considering the combined risks in the changing environment, especially given recession-predicted economic, practical evidence is needed.

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