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Impact of Environmental Pollutants on Alzheimer's Disease: A Review

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ABSTRACT

Environmental pollution is one of the major concerns as it affects public health and is responsible for various neurological disorders too. Neurological disorders are governed by many different factors - they can be genetic, based on lifestyle, or environmental. In many recent studies, it has been observed that exposure to many environmental pollutants increases the risk of Alzheimer's disease (AD). Pollutants like PM_{10}, $PM_{2.5}$, and some other ultrafine nanoparticles, lipophilic vaporized toxicant (acrolein) can easily reach the brain by crossing the blood-brain barrier after it they can activate the innate immune responses inside the target site like neurons, astrocytes, and microglia by this way they can be neurotoxic. Human epidemiological evidence proves that there is a correlation between environmental pollutants and neurological disorders like dysfunction of mitochondrial, oxidative stress, disruption in the myelin sheath, the blood-brain barrier anatomy alterations, and endoplasmic reticulum stress which direct towards cognitive impairment with lower quality of lifestyle. The review article aims to culminate the correlation between the environmental factors and Alzheimer's disease, The different sources of pollution and their effect on various stages of human life, developmental neurotoxicity, and neurological disorders also have been discussed.

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INTRODUCTION

Alzheimer's disease is called elderly dementia as it is responsible for 60–70% of global cases. This debilitating is progressive, and it is an irreversible illness (McKhann et al. 2011) According to WHO it is a global public health issue. Environmental air pollutions are responsible for neurotoxicity related to development, and for the teratogenic effect. Eventually, it becomes a cause of mental retardance or just a reduction in IQ level, or both. The exact process of how pollution induces neurotoxicity is still unknown but it is clear that it interferes with an inflammatory pathway (Akt/GSK3β, Nrf2/NF-k, and MAPKs/PI3K), modulates the neurotransmitters, and affects the endogenous antioxidant defense system too (Iqbal et al. 2020). Etiologically the relation between AD and environmental pollution is still not clear but in pathology, it is heavily acknowledged (Mir et al. 2020). German physician Aloe Alzheimer originally described Alzheimer's disease in 1907 (Prince et al. 2016). He conducted years of research on two patients who exhibited hallucinations, aggression, and cognitive problems. Since 1907, there has not been a single treatment available to change AD. A summary of its pathology, epidemiology, and genetics is provided in this article. After it, further therapy opportunities and upcoming remedial approaches will be taken into account (Sharma et al. 2020). According to epidemiological proof, education and physical fitness can act as a safeguard but diseases like diabetes in middle age and hypertension too can increase the risk of Alzheimer's disease (Xu et al. 2015). Research showed that obesity increases the risk of Alzheimer's disease and dementia but recently this was challenged (Qizilbash et al. 2015). Vascular risk factors can increase the risk of AD by a "double-hit" of superimposed cerebrovascular injury. It can also be possible that if there is any vascular damage that can affect the progress of pathology of Alzheimer's disease directly (Van Norden et al. 2012)

ENVIRONMENT POLLUTANTS RESPONSIBLE FOR ALZHEIMER'S DISEASE

Air pollutants especially particulate matters increase the risk of oxidative stress, and hypertension, resulting in dementia and cognitive decline (Peters et al. 2019) Lancet commission (Commissions from the Lancet journals) in 2017 included air pollution in the list of responsible factors for dementia

(Livingston et al. 2017). Various pieces of evidence (Listed in Table 1) prove that pollutants like ozone, NO_2, and particulate matter are responsible to decrease cognitive strength and increase the case of dementia and Alzheimer's disease.

MECHANISM OF EXPOSER AND EFFECT ON BRAIN HEALTH

As part of the mechanism of neurodegenerative illness, oxidative stress, inflammation, protein aggregation, and dysfunction in mitochondrial neurons all play a role (Genc et al. 2012) (Fig.1). A study on a dog was conducted in Mexico City (highly polluted). The dog was living in a highly polluted area for a long time. The study observed high brain inflammation (Calderon et al. 2002). The progression of oxidative stress involves the mechanisms of neurological disturbances and it can be caused by pollution (Calderon et al. 2002, Peters et al. 2006). Air pollution is a mixture of gasses and some other factors like PM_{10} and $PM_{2.5}$ (Costa et al. 2017). $PM_{2.5}$ have the ability to translocate up to the alveolar region. From the alveolar region, it merges with the systemic circulation and finally reaches the brain (Costa et al. 2019). The ultrafine particulate matter (UFPM), which has a size <100 nm is more harmful as because of its size it can easily enter into the systemic circulation. They can reach up to the brain via the olfactory bulb or the other way through the blood-brain barrier (Costa et al. 2017, Iqbal et al. 2018). After translocating across the CNS, they activate the innate immune responses, which activate microglia and increase lipid peroxidation. Because of it, patients suffer from neuroinflammation specifically in the cortex and hippocampus (Morris-Schaffer et al. 2019). The exact pathway of neurotoxicity induced by air pollution is still unknown; but, few studies suggest nanoparticles interference in the alteration of the amyloid-beta process and neuroinflammation (Oudin 2020).

EVIDENCES ABOUT ALZHEIMER'S DISEASE AND POLLUTION

In other published studies including people (who took part in the third National Health and Nutrition Examination Survey; NHANES III; USA) aged 18 to 59, it was found that there was only a weak correlation between reaction time,

Table 1: Effect of pollutants on cognitive health.

Pollutants	Air Quality Standards			Summary	Reference
	India: Air Quality Standards		WHO: Ambient (outdoor) air pollution Industrial, Residential, Rural, and Other Area		
	Industrial, Residential, Rural, and Other Area	Ecologically Sensitive Area (notified by Central Government)			
$PM_{2.5}$	40 $\mu g.m^{-3}$ annual mean 60 $\mu g.m^{-3}$ 24-hour mean	40 $\mu g.m^{-3}$ annual mean 60 $\mu g.m^{-3}$ 24-hour mean	20 $\mu g.m^{-3}$ annual mean 50 $\mu g.m^{-3}$ 24-hour mean	The study suggested that the cognitive decline rate is higher in women who live in a polluted areas where the level of PM2.5 is higher. In the long-term exposure rate of cognitive decline per 10 $\mu g.m^{-3}$. No correlation could be found between one month, one to two months, or 2 or 5 years of exposure.	Weuve et al. (2012)
PM_{10}	60 $\mu g.m^{-3}$ annual mean 100 $\mu g.m^{-3}$ 24-hour mean	60 $\mu g.m^{-3}$ annual mean 100 $\mu g.m^{-3}$ 24-hour mean	20 $\mu g.m^{-3}$ annual mean 50 $\mu g.m^{-3}$ 24-hour mean	The study was conducted on participants who did not move to London during the study. According to this study PM_{10} exposure (with a 4-y lag) is linked with cognitive decline.	Tonne et al. (2014)
NO_2	40 $\mu g.m^{-3}$ annual mean 80 $\mu g.m^{-3}$ 1-hour mean	30 $\mu g.m^{-3}$ annual mean 80 $\mu g.m^{-3}$ 1-hour mean	40 $\mu g.m^{-3}$ annual mean 200 $\mu g.m^{-3}$ 1-hour mean	An increased interquartile concentration of NO_2 is directly associated with dementia risk.	Chen et al. (2017)
O_3	100 $\mu g.mL^{-1}$ per 8 hour 180 $\mu g.m^{-1}$ per hour	100 $\mu g.mL^{-1}$ per 8 hour 180 $\mu g.m^{-1}$ per hour	100 $\mu g.m^{-3}$ 8-hour mean	A study was conducted based on CDR-SB assessments and MMSE (p<0.05). In this study, participants were exposed to the highest and medium O_3 as a result of cognitive decline triggered.	Cleary et al. (2018)

visual-motor coordination, and learning with an increment of annual Particulate Matter 10(PM_{10}) levels. (cardiovascular risk factors, many markers of socioeconomic status, and ethnicity are adjusted.) (Chen & Schwartz 2009). Another study (in which N=780) was conducted on non-Hispanic black and white people in which the age group was 55 and older. It was observed that the older adults who were living in the areas where the concentrations of $PM_{2.5}$ were high, had an error rate 1.5 times higher than the people who were living in lower concentrations (Ailshire & Crimmins 2014). One more finding suggested that long-term exposure to pollution can cause Alzheimer's disease in elderly people (Calderón-Garcidueñas et al. 2004). Small particles are more dangerous for cognitive performance than larger ones. It can be because they have more chances to reach the brain than larger ones as they have a smaller size (Zeng et al. 2010).

A postmortem study on a dog suggested that air pollution affects the brain by creating neurotoxicity and histological aberration, especially in the cortex region, histological damage can be easily marked. Neuroinflammation and neurodegeneration are also marked (Calderon-Garciduenas et al. 2003). In Alzheimer's disorder etiology, there are many other factors responsible like certain kinds of head injury, genetics aging, different environmental metabolites, and substances.

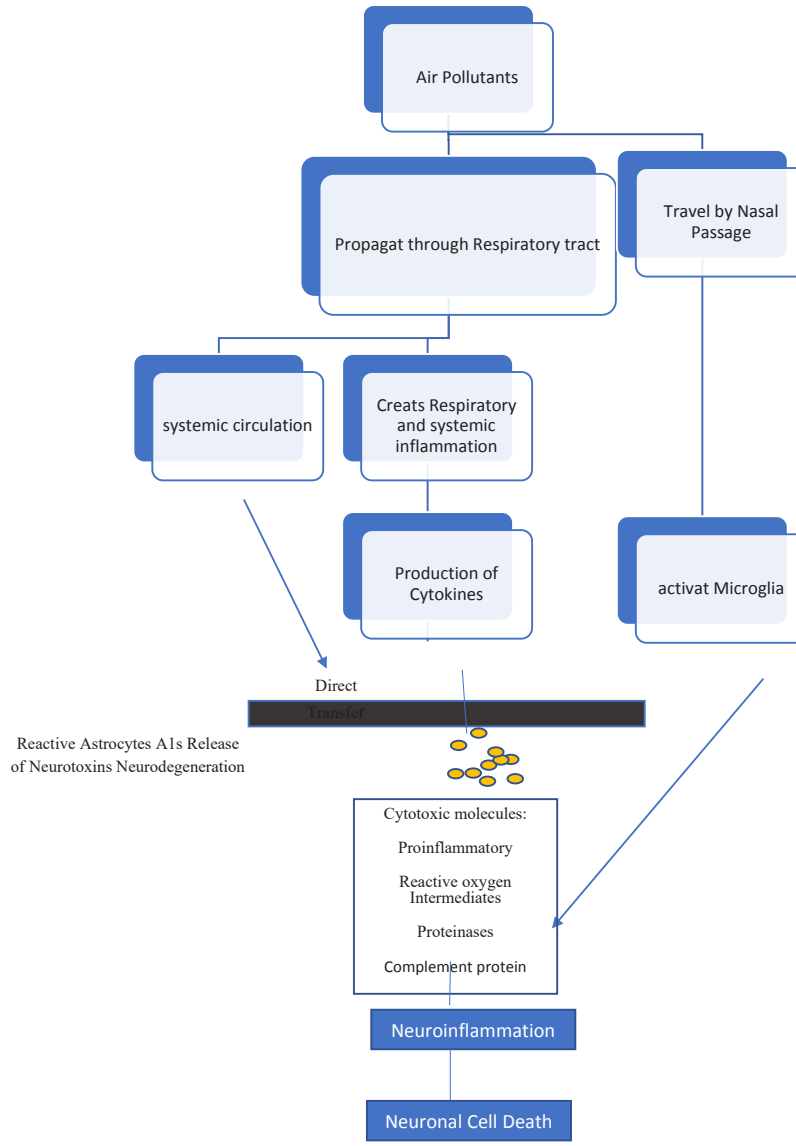

Fig. 1: Effect of air pollutants on brain.

(Coon et al. 2007, Calderon-Garciduenas et al. 2004, Guo et al. 2000). This fact is already known that AD is affected by genetic elements. AD is correlated with the APOE-E4 allele predominantly. Because the environmental element is still poorly understood, there is a connection between the delay in exposure to Alzheimer's disease and the onset of AD. However, due to the time delay between exposure and the role of environmental factors, their function in AD is not well known (Coon et al. 2007, Rahman et al. 2020).

Research indicates that genetic predisposition accounts for 70% of AD cases, whereas the remaining 30% are caused by lifestyle-related problems including obesity, hypertension, smoking, etc. (Ballard et al. 2011). All environmental pollutants and toxins are not responsible for Alzheimer's disease, neurotoxins found in the environment are responsible for neurological issues in elderly people (Baldi et al. 2003). However, research is needed in the field that environmental pollutants are alone responsible for the progress of AD or a combination of being responsible.

EFFECT OF AIR POLLUTANTS ON THE PROGRESSION OF ALZHEIMER'S DISEASE

Due to metabolic imbalance oxidative stress generates and as a result free radicles accumulate in the body which leads to problems like neuroinflammation and neuropathology (Block & Calderón-Garcidueñas 2009). Many studies suggested that $PM_{2.5}$ and PM_{10} play a very important role in AD and other neurodegenerative disorders causation. Metals such as nickel, lead, and gases like sulfur-di-oxide, carbon-mono oxide, and nitrogen oxide may play an important role in the production of ROS (reactive oxygen species) and can cause oxidative stress cerebrovascular damage, neuroinflammation, accumulation of Aβpeptide which is a major contributor in the progression of to AD (Moulton & Yang 2012). It is reported that the brain of mice which was exposed to Ni (nickel) showed increased amyloid-β40 and amyloid-β42thesr both are associated with Alzheimer's disease (Kim et al. 2012). A study on children conducted in Mexico City showed that when children get exposed to pollutants, a protein starts depositing inside their body which is analogous to the protein found in the early stages of Alzheimer's disease (Calderon-Garciduenaset al. 2004). In another study, it is reported that 56% of children who were exposed to PM at a younger age had white matter lesions which can cause neurodegeneration and neuroinflammation in upcoming stages of life (Kim et al. 2012). Exposure to these particles can cause neuro-inflammation because of the activation of the sensor of the ROS pathogen (Calderón-Garcidueñas et al. 2012). Hippocampus is a commonly affected area in the brain that is affected by AD. Adult Wistar rats show heavy progressive neuro degradation when exposed to O_3, In the inflammation process, it disrupts ROS, and minimizes hippocampus repair (Rivas-Arancibia et al. 2009). It is shown in a study that in humans and animals, the expression of neurodegenerative disease pathology-linked makers increases with the organic compound, PM_{10}, gases, and $PM_{2.5}$ (Costa et al. 2017). Many epidemiological, experimental, observational, and clinical studies suggested that air pollution can cause the disease related to CNS and AD is one of them (Genc et al. 2012). Laboratory experiments have proved that many VOCs such as toluene, ketone, and benzene can perform biochemical and morphological changes in neurons eventually which can be a cause of AD. (Kukull et al. 1995). Results from chromatography and mass spectrometry show that AD patients have higher levels of VOCs than normal patients when compared to those without the disease (Tisch et al. 2013).

NANOPARTICLES EXPOSURE TO ALZHEIMER'S DISEASE

Epidemiologically there is no study to correlate nanoparticles exposure to Alzheimer's disease, but according to experimental evidence, it is proved that NP has a role in neurological disorders. Recently, it was discovered in a study on mice that giving Tio2-NPs to them through their noses causes glios and oxidative stress. Other impacts include a decline in the number of neurons in the hippocampus that are connected to cognition and memory due to neuronal death (Ze et al. 2014). When male and female mice were

Table 2: Air pollutants Responsible for AD Progression.

Air pollutant	Dose	Sample size	Summary of the experiment	References
PM and O_3	1mg.m^{-3} Ni and NP were given through inhalation. Ozone exposure dose was 0.25 ppm.day^{-1} up to 4h.	Male and Female mice were used Control n = 5 Exposed n = 11 male = 6 female = 5	Rapid doubling of amyloid-ß40 affected the repairing system of the brain	Rivas-Arancibia et al. (2009), Kim et al. (2012)
VOCs	Exposed Occupationally	Male Wistar rats: g were chosen AD n = 193 Control n = 243	AD developed	Kukull et al. (1995)

Table 3: Some research pieces of evidence showing the change in cognitive behavior due to air pollution.

Title of the Study	Findings	References
Association between Traffic-Related Air Pollution in Schools and Cognitive Development in Primary School Children: A Prospective Cohort Study	The polluted area has seen a small cognitive development in school children as compared to the non-polluted area.	Sunyer et al. (2015)
Association of Traffic-Related Air Pollution with Children's Neurobehavioral Functions in Quanzhou, China	Children studying in schools in polluted areas had fewer marks in testing cognitive, sensory, motor, and psychomotor functions than those studying in non-polluted areas.	Wang et al. (2009)
Impact of short-term risk to ambient air pollution on cognitive performance and cognitive air pollution on human capital formation.	The conclusion was that PM_{10}, $PM_{2.5,}$ and CO Exposure reduced the test scores of high school students in Israel.	Lavy et al. (2014)
Neurobehavioral performance in adolescents is inversely associated with traffic exposure.	The study suggested an opposite relationship between the ability to pay attention in a group of 606 teenagers and traffic contact.	Kicinski et al. (2015)
Longitudinal relationship between air pollution risk in school and cognitive development among schoolchildren over a period of 3.5 years.	A study found 3.5 years were between exposure to air pollution at longitudinal Association School and the development of cognitive health in school-going children.	Forns et al. (2017)
Traffic-related air pollution and cognitive function in a platoon of older men.	It was observed in the old people that ambient air pollution which was related to traffic is associated with the decline in cognitive functioning in older men.	Power et al. (2011)
Exposure to air pollution and cognitive decline in older women.	The study was about cognitive decline regarding the relationship between PM_{25} and PM_{10}.	Weuve et al. (2012)
Residential proximity to the nearest major roadway and cognitive function in community-dwelling seniors: results from the MOBILIZE Boston Study	The study cleared that people who live close to the road get a 34% more chance of scoring less in MMSE (the study population was ~ 77 years old). According to the study, the proximity of the road was directly linked to psychomotor speed, oral learning and memory, executive functioning, and language reduction.	Wellenius et al. (2012)
Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study	A large population-based study in which people living near the road were at a higher risk of dementia, but not Parkinson's disease.	Chen et al. (2017)
Components of air pollution and cognitive function in middle-aged and older adults in Los Angeles.	In a study of 1496 older healthy and middle-aged people that specific components in ambient air pollution are associated with low cognitive abilities.	Gatto et al. (2014)
Exposure to ambient air pollution and dementia events: a population-based platoon study	In a population-based study that involved residents in Ontario (Canada), 55–85-year-old authors studied the population. In which it was exposed to air pollution even at relatively low levels related to a high risk of insanity.	Chen et al. (2017)
Fine particulate matter air pollution and cognitive function among older adults in the US.	The study was on adults aged 50 ~ who were living in areas where $PM_{2.5}$ was higher. It was observed that they had a worse cognitive function, especially in concern of the relevant memory component.	Ailshire and Clarke (2014)

treated with nanoparticles of Al, Cu, and Ag multiple times various alterations like motor deterioration, sensory, and cognitive were recorded in their brain. (Sharma et al. 2009, Shanker Sharma & Sharma 2012). When mouse neuro-2a and human (SK-N-SH) neuroblastoma cells were exposed to silica nanoparticles, the A level of (intracellular) both cell lines increased, and the APP level increases with a decrease in NEP protein level. The whole process was mediated with the help of increased ROS production (Yang et al. 2014). In another study when Neuro 2a cells were treated with silver nano-particles, they exhibited the deposition of Aβ plaques and the expression of APP enhanced, but NEP and LPR1 expression was reduced which directly says that silver NPs alter the amyloidogenic pathway as a result of AD chances get increased (Huang et al. 2015)

CONCLUSION

In the Progression of AD, environmental toxicant has an important role and are important for public health. But some chemical agents will be always in the limelight. Many inorganic and organic compounds have a direct or indirect link

with AD. but in the lack of direct evidence, all these things are just elusive. As there are other factors contributing to the genesis of AD, the neurotoxic chemical has to be further examined for its potential role in AD. Experimental research and data demonstrate the fact that there are potential risks associated with exposure to various environmental contaminants. These pollutants and oxidative stress production show a similar toxicity mechanism. Both of these represent typical neurodegenerative disease mechanisms. If oxidative stress is caused by the creation of ROS or antioxidant enzymes that disrupt a few proteins, such as α-syn, Aβ, and Tau. As a result, the cerebral cortex and hippocampus of AD patients lose neurons.

Due to these neurotoxins, oxidative stress generates which inhibits various enzymes in pathways that are involved in the accession of various noxious materials in many neural cells including Aβ, byproducts of oxidative aberrant proteins, and DNA oxidation which can alter regulations (epigenetic/genetic). Chemicals related to AD exposure will continue in the future also as they are commercially in use and an essential service also but awareness can be one of the weapons against it. Research is also needed in the field of biomarkers related to this field so that early diagnosis can be possible. There is also a need for epidemiological study in this field.

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ABBREVIATIONS

$PM_{2.5}$: Fine particles with a diameter of 2.5 microns (μm) or less
NO_2: Nitrogen dioxide
PM_{10}: Coarse particles with a diameter of 10 μm or less
PM: Particulate matter
AD: Alzheimer's Disease

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