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Review Article

Environmental Pollutants and Their Impact on Prenatal Brain Development and Later Neurodegenerative Diseases

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Article Info

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ABSTRACT

Background: Neurodegeneration is the progressive loss of neurons' structural and functional components, a common feature of many neurodegenerative disorders. Its neurological side effects may significantly impact patients' mental and physical health. Due to their widespread prevalence, some neurodegenerative pathologies have gained international attention in recent years. Although its etiology is not fully known, it is suggested that environmental factors and genetic predisposition are responsible. Understanding the mechanisms that drive the development of neurodegenerative diseases will allow the development of new therapeutic strategies for their prevention and treatment. In particular, the postnatal effects of prenatal exposure have been investigated for many years. **Summary:** It has been long known the role of pregnancy-related factors on brain development and the impact of intrauterine changes on the development of many neurodegenerative diseases. The main mechanisms crucial in neurodegeneration are loss of neuronal function and cell death. Currently, the drugs used in the treatment of neurodegenerative diseases are used for symptomatic treatment and cannot stop the process of neuron loss. Identifying molecular commonalities of neurodegenerative diseases will help discover effective drugs for treating neurodegenerative diseases in the future. **Key Messages:** This review provides a comprehensive overview of the role of environmental neurotoxic exposures on prenatal neurodegeneration, the specific sensitivity of the nervous system to toxicant exposure, and the mechanisms of neurodegeneration. In a pathophysiological context, deciphering these mechanisms of prenatal neurodegeneration contributes to the discovery of therapeutic targets.

ÖZET

Arka Plan: Nörodejenerasyon, birçok nörodejeneratif hastalığın yaygın bir özelliği olan nöronların yapısal ve fonksiyonel bileşenlerinin progresif kaybıdır. Bu durumun nörolojik yan etkileri, hastaların mental ve fiziksel sağlıklarını önemli derecede etkileyebilir. Yaygın prevalansları nedeniyle bazı nörodejeneratif patolojiler son yıllarda uluslararası ilgi görmüştür. Etiyolojisi tam olarak bilinmemekle birlikte, çevresel faktörlerin ve genetik yatkınlığın bu duruma neden olduğu öne sürülmektedir. Nörodejeneratif hastalıkların gelişimini tetikleyen mekanizmaların anlaşılması, bunların önlenmesi ve

tedavisi için yeni tedavi stratejilerinin geliştirilmesine olanak tanıyacaktır. Özellikle, prenatal maruziyetin postnatal etkileri uzun yıllardır araştırılmaktadır.

Özet: Gebelikle ilgili faktörlerin beyin gelişimindeki rolü ve intrauterin değişikliklerin birçok nörodejeneratif hastalığın gelişimi üzerindeki etkisi uzun zamandır bilinmektedir. Nörodejenerasyonda kritik olan ana mekanizmalar, nöronal fonksiyon kaybı ve hücre ölümüdür. Şu anda nörodejeneratif hastalıkların tedavisinde kullanılan ilaçlar semptomatik tedavi için kullanılmakta olup, nöron kaybı sürecini durdurmamaktadır. Nörodejeneratif hastalıkların moleküler ortak yönlerinin belirlenmesi, gelecekte bu hastalıkların tedavisi için etkili ilaçların keşfedilmesine yardımcı olacaktır.

Ana Mesajlar: Bu derleme, çevresel nörotoksik maruziyetlerin prenatal nörodejenerasyon üzerindeki rolü, sinir sisteminin toksinlere karşı özel duyarlılığı ve nörodejenerasyon mekanizmalarını kapsamlı bir şekilde incelemektedir. Patofizyolojik bir bağlamda, prenatal nörodejenerasyonun bu mekanizmalarının çözümlenmesi, terapötik hedeflerin keşfine katkıda bulunmaktadır.

1. INTRODUCTION

Most neurological diseases have a solid link to exposure to environmental agents during and after pregnancy. When the relationship between neurological diseases and prenatal conditions is examined, it is seen that prenatal exposure is the most important factor.The mother's surroundings impact the developing fetus since, throughout the in-utero stage, the fetus is solely exposed to the mother's body. Dopaminergic neurons are lost during pregnancy due to exposure to bacterial endotoxins, lipopolysaccharide (LPS), and heavy metals. (ii) Another factor is dietary exposure. Eating patterns significantly affect physiology and metabolism. High-iron-content foods cause neurodegeneration in the midbrain. Dopaminergic neurons appear to shrink. Metal exposure is also among the factors that cause neurological problems. Toxic contaminants called heavy metals are released into the environment. They are widespread in the environment and poison living systems as they build up. The blood-brain barrier (BBB), which prevents the function of metal-protein complexes that play a barrier role in transporting heavy metals from the systemic circulation to the brain and showing the toxic effects of metals, protects tissues from metal toxicity. Heavy metal lead (Pb) is renowned for its detrimental effects on the nervous system. Heavy metals with a strong potential for neurotoxicity are mercury (Hg). Inorganic arsenic (As) is a neurotoxic metalloid that negatively impacts neurodevelopment and cognitive function . Another harmful heavy metal linked to brain alterations, including memory loss and mental retardation, is cadmium (Cd). A neurotoxic substance called aluminum (Al) has a role in the pathogenesis of neurodegenerative diseases. An essential element that has critical physiological roles in maintaining cellular homeostasis is manganese (Mn). Parkinson's disease (PD) has been linked to Mn exposure. The transferrin and the divalent metal transporter 1 (DMT1) receptors allow the necessary element, iron (Fe), to be delivered to the brain. Epidemiological research has determined that Fe raises the possibility of developing Parkinson's. It is among the agents that cause Alzheimer's disease (AD) and PD, especially after exposure to pesticides.Insecticides, herbicides, and fungicides are essential examples of pesticides. More often, insecticides like organophosphates, organochlorines, and carbamates are utilized. A common herbicide called paraquat (PQ) can cause AD. PD is linked to the organophosphate pesticide rotenone. Lifestyle factors such as smoking, drinking, and drug abuse are important factors that negatively affect the health and well-being of the organism. The prevalence of neurodegenerative illnesses is rising along with a sedentary lifestyle and lack of exercise. Furthermore, it has been noted that substances like cocaine, heroin, and the commonly abused methamphetamine (MA)

decrease the formation of the myelin essential protein in the optic nerves and increase the number of malformed axons, mean optic fiber area, and lamellarity. Due to commercial uses of solvents in things like metal degreasing, dry cleaning, paint thinner, and detergent ingredients, solvents are widely used. Some solvents are readily absorbed by the peripheral and central nervous systems (CNS) because they are lipophilic. N-hexane and toluene exposure causes severe cases of Parkinsonism. One particular solvent whose capacity to promote neurodegeneration has been thoroughly investigated is trichloroethylene (TCE). (vii) Nanoparticles (NPs): With a diameter of approximately 100 nm are incredibly tiny molecules. NPs can cross the BBB because of their small size, allowing them to enter the body through various other entry points and eventually induce neurotoxicity, neuroinflammation, and neurodegeneration in the CNS. Mechanisms of environmental factors inducing neurodegeneration include oxidative stress formation, activation of glia-induced neuroinflammation by increasing reactive oxygen species (ROS) production and by releasing antioxidant enzymes and promoting the formation of protein aggregates such as β-Amyloid (Aβ), Tau, or α-syn.

1.1. Neurodegeneration

Neurodegenerative diseases are characterized by the progressive loss of structure or function of neurons, including neuron death, and spread to other organs in later stages. PD, AD, Batten disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and Huntington's disease (HD) are the most prevalent neurodegenerative diseases [1-6].

Several studies have suggested that the most crucial underlying cause of degenerative disorders is neurodegeneration [7-9]. The effects of neurodegeneration on patients can have serious adverse effects on mental and physical health. Environmental characteristics are considered significant factors contributing to neural dysfunction-related disorders. Exposure to environmental agents that cause neurological diseases develops as a result of prenatal and postnatal exposure. Some neurotoxic metals such as As, chromium (Cr), Pb, Cd, Hg, Mn, and Al as well as metal-based nanoparticles and pesticides, also play a role. These agents cause the production of neurofibrillary tangles (NFTs), amyloid, or senile plaques, which are hallmarks of neurological dysfunction. Additionally, exposure to solvents also has a significant contribution to the development of neurodegeneration [10,11].

1.2. Prenatal conditions

The connection between neurons and glial cells is extremely critical during pregnancy and after birth until the age of three. It has been proven that many epigenetic factors that are effective during pregnancy (including fetal hypoxia, premature birth, infection, inflammation, stress, malnutrition, developmental delay, low birth weight, hypertension, anemia, diabetes, and medications) play a role [12-14] (Figure 1). Data obtained from current literature show that stopping the spread of neurodegenerative diseases at the beginning of life should be defined as the only method to prevent neurodegeneration. The "two-hit" hypothesis, first proposed for PD and other human neurodegenerative pathologies, including AD, covers the intrauterine periods. The initial blow to the nervous system occurs early in life. It causes a risk of developing PD or AD later in life, depending on the resilience of the brain or the susceptibility to developing neurodegeneration later in life [7,8,12]. Prenatal exposure of the mother or the fetus to neurotoxic agents can affect the CNS, inhibiting normal neuronal development processes or preventing the brain from fully

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functioning [13]. Adverse effects on the CNS before birth also negatively impact cognitive functions in early childhood. Maternal use of cocaine or alcohol during pregnancy causes a decline in cognitive functions and an increase in psychopathologies in childhood. In addition, it has also been associated with substance use disorders in later life [15]. It has been suggested that even dementia is triggered by adverse prenatal conditions [16,17].

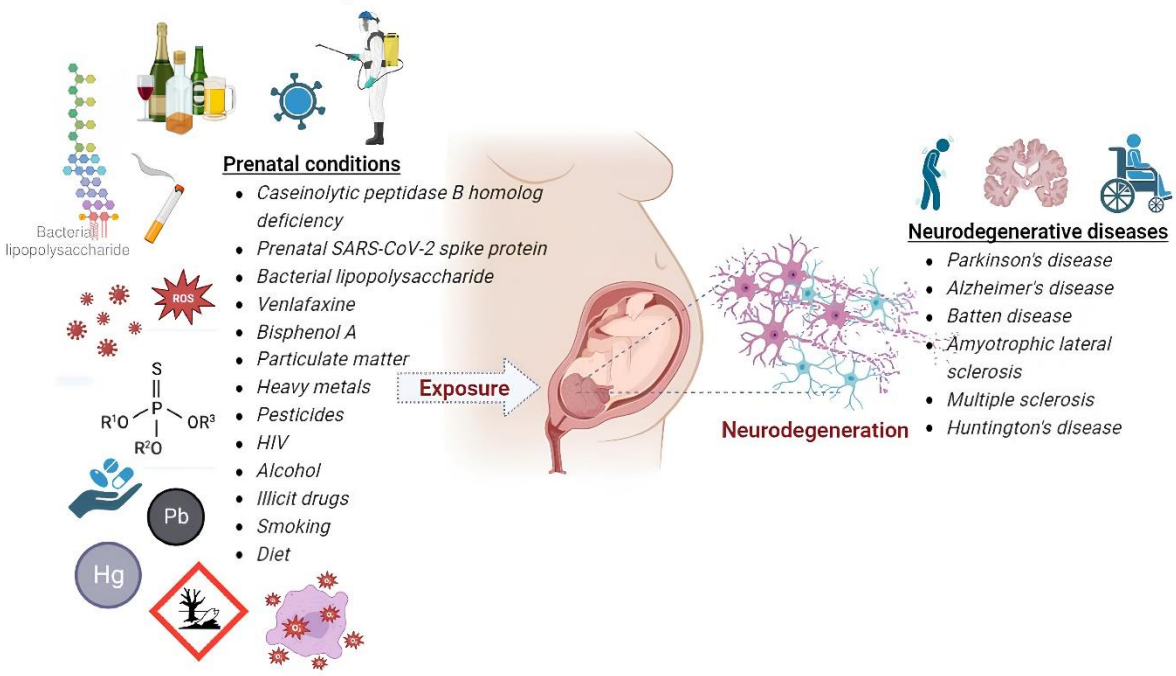

Figure 1. Environmental neurotoxic exposures on prenatal neurodegeneration.

1.3. Caseinolytic Peptidase B Homolog Deficiency

Caseinolytic peptidase B homolog (CLPB) is mitochondrial inner-membrane protein highly expressed in the brain. In 2015, a novel mitochondriopathy due to CLPB deficiency is identified as a cause of severe neonatal encephalopathy. . In other words, CLPB deficiency is a mitochondriopathy in which hyperlactatemia, white matter changes, and 3-methylglutaconic aciduria are observed. As a result of the mitochondrial localization of the CLPB protein, the enrichment of the CLPB protein in the mitochondrial proteome in various tissues, especially the brain, was supported by proteomic experiments. Therefore, in CLPB deficiency, severe brain damage is accompanied by multisystem involvement. Prenatal problems such as fetal growth restriction, polyhydramnios, and decreased or increased fetal movements occur in babies. They are born with severe neurological disorders with general hyperekplexia, hypertonia, respiratory failure, febrile seizures, and ventilator dependence. These neurological findings damage nerve pathways. The degeneration of the deep white matter protecting subcortical areas causes pathological findings. A strong presence of astrogliosis is observed in regions with degeneration. Reactive microgliosis consists of hyperbranched active microgliocytes that cluster widely in damaged areas. In brain regions where damage is intense, there is a significant decrease in chromatin condensation and marked white matter vacuolation, myelin density, strong astrogliosis, reactive microgliosis, and degradation of white matter due to death of oligodendrocytes are observed. White matter changes and a mitochondrial leukoencephalopathy-like condition were observed in a case with CLPB deficiency. Cortical and deep gray matter involvement (brainstem, globus pallidus, cerebellum, amygdala, dentate nucleus, and hippocampus),

cortical thinning, and significant decrease in neuron density were detected. CLPB deficiency triggers mitochondrial dysfunction and accumulation of protein aggregates, resulting in decreased mitochondrial energy production, apoptosis, vasoconstriction, and oxidative stress. The neurodevelopmental disorder associated with CLPB deficiency is characterized by facial dysmorphism. Dysmorphic faces include microcephaly, prominent eyes, ocular hypertelorism, broad nasal bridge, bulging nose, tented upper lip with microform cleft, micrognathia, and low-set backward-pointed ears. Interestingly, the absence of congenital cataracts supports that this anomaly is a variable feature unrelated to the severity of neurological involvement. In addition to all these effects, postmortem neuropathological examinations revealed widespread subependymal white matter loss, severe frontal cystic leukoencephalopathy, striate-thalamic neurodegeneration, and intense reactive astrogliosis observed in the fetus with CLPB deficiency [18].

1.4. SARS-CoV-2 Spike Protein

SARS-CoV-2 spike protein persisted in the skull-meninges-brain axis of COVID-19 patients. The presence of spike protein causes pathological and behavioral changes in the mouse brain. Spike protein exacerbates neurological damage in mice by increasing brain sensitivity [19]. Recent studies have found that the COVID-19 virus significantly affects embryonic organs, including the brain. It has been suggested that the SARS-CoV-2 spike protein is associated with neuroinflammation and that exposure to SARS-CoV-2 spike protein during pregnancy may mediate the development of autism in children. In a study conducted with male and female rats exposed to COVID-19 spike protein, it has been observed that male rats are more sensitive than female rats and have significant histological, biochemical, and behavioral changes in their brains. Neuroinflammatory changes are triggered, causing a progressive decrease in neuron numbers and cerebellum damage [20]. SARS-CoV-2 enters human cells by interacting with specific membrane cell receptors, such as the angiotensin-converting enzyme 2 transmembrane receptor, and activating the SARS-CoV-2 spike protein through cleavage of transmembrane serine protease 2. The first case of SARS-CoV-2-associated meningitis was reported, in which the virus was found in the nervous system [21].

1.5. Bacterial Lipopolysaccharide

SARS-CoV-2 spike protein and transcripts in the postmortem brain suggest that the virus directly causes CNS infection. SARS-CoV-2 spike protein can readily cross the BBB when injected intravenously. This indicates that the S1 protein translocating to the brain parenchyma may affect cognitive processes and brain functions, contributing to psychiatric and neurological COVID-19 symptoms [22]. In conclusion, prenatal exposure to SARS-CoV-2 negatively affects the neurodevelopmental process [23].

In pregnant rodents, maternal immune activation (MIA) has long-lasting effects on the offspring, with abnormalities in gene expression, histology, and behavior that are reminiscent of autism and schizophrenia [24]. In a study, STAT1 target genes were observed to be downregulated in MIA microglia exposed to systemic lipopolysaccharide (LPS) during adulthood [25]. Changes in microglial gene expressions in microglia with LPS-induced maternal immune activation have been associated with a decreased immune response, including interferon signaling and metabolic changes. Similar microglial changes have previously been reported in humans and animal models in neuropsychiatric and neurodegenerative conditions [26,27]. For example, activation of the prenatal immune system has been associated with the risk of developing schizophrenia in later life [28]. Environmental agents that affect microglia contribute to various

neurological diseases throughout life, depending on the week of pregnancy to which the fetus is exposed and whether the fetus is at a susceptible period of development [24].

1.6. Venlafaxine

Although venlafaxine appears to be a new antidepressant with better efficacy, safety, and tolerability in typically depressed individuals, it has been observed to cause fetal-developmental neurotoxicity when used by pregnant mothers in cases of prenatal depression. However, no obvious neurodevelopmental and neurobehavioral problems were observed in the baby [29]. A clinical study found no effect of venlafaxine on children's behavioral and intellectual outcomes [30]. However, opposite results were found in different research groups [31]. Administration of venlafaxine to rats during pregnancy has been shown to cause spontaneous abortions [32], premature birth, an increased number of stillbirths [33], and changes in the cardiovascular system [34]. A study in rats found that prenatal treatment with therapeutic doses of venlafaxine caused apoptotic neurodegeneration and neurocytoarchitectural damage in the hippocampus and striatum regions of the fetal brain during the sensitive periods of brain development of rats. It should not be overlooked that it causes mental and cognitive disorders as well as depressive-like behavior. Therefore, most antidepressants, including venlafaxine, have risks for both the fetus and the expectant mother [35].

1.7. Bisphenol A

Bisphenol-A (BPA) is used primarily in the plastic industry, and it is one of the agents that negatively affects human health and causes neurotoxicity. In animal studies, researchers have suggested that BPA reduces the differentiation and proliferation of neural stem cells (NSCs), disrupts mitochondrial protein transport and myelination, and causes cognitive problems and excessive mitochondrial fragmentation [36]. Low-level BPA exposure reduces hippocampal neurogenesis, leading to memory loss and learning disability [37]. Exposure to BPA triggers oxidative stress by inducing ROS formation, leading to neuron death [38-40]. A severe concern arises during pregnancy: BPA can pass through the placenta, negatively affecting brain development and fetal growth [41]. Exposure to environmental pollutants such as hazardous chemical compounds, harmful heavy metals, pesticides, and solvents causes deleterious changes in hippocampal neurogenesis [42-44]. For this reason, learning and memory functions related to the hippocampus are negatively affected. Exposure to BPA during developmental stages inhibits hippocampus-derived neurogenesis in the brain [36,45,46].

1.8. Particulate Matter

Air pollutants are believed to affect the CNS through several mechanisms. It affects directly through the transport of contaminants to the CNS or indirectly through systemic inflammation. After PM reaches the circulatory system, it negatively affects the CNS by creating a systemic inflammatory response. Proinflammatory mediators contributing to neuroinflammation and tissue loss have been detected in brain regions such as blood, cerebrospinal fluid, olfactory bulbus, frontal cortex, and hippocampus. Studies show that PM10 exposure triggers the expression of genes related to inflammation and oncogenesis in rat brains [47,48]. Polycyclic aromatic hydrocarbons (PAHs) are compounds with mutagenic, teratogenic, highly toxic, immunotoxicogenic, and carcinogenic effects that arise from incomplete combustion of organic compounds. PAHs enter the human body through the inhalation of air, drinking water, consumption of

contaminated foods, and cigarette smoke, causing mutations in DNA. Prenatal exposure to PAHs causes regression in neurocognitive development [49]. Neurodevelopmental deficits associated with prenatal PM exposure in children include attention and differences in cognition behavior [50]. Postulated mechanisms for PAH-induced neurotoxicity are related to the disruption of pathways that regulate synapse plasticity, formation, and neuronal differentiation [51]. The effect of prenatal PAH exposure on childhood IQ has been investigated in many studies [51-53]. Different results were found in the studies. Contrary to studies claiming it harms IQ [52], another study showed no relationship between prenatal PAHs measured in cord blood and the child's IQ [53]. The amount of PAH exposed through nutrition constitutes a significant portion (70-90%) of total PAH exposure. There is sufficient evidence that prenatal PAH exposure negatively affects memory, a child's intelligence, average overall development, mental development, and verbal IQ and causes anxious and depressive behavior [49].

The negative impact of polluted air on cognition in young children may occur due to exposure while still in the womb. Exposure to PAHs can cause decreased scores on the Bayley scale of infant development (BSID-II) and a decrease in verbal intelligence and IQ in children under five [53,54]. Another study reported that high-concentration PAH exposure caused a decline in verbal and non-verbal IQ scores [55].

In addition to PAH, in-utero exposure to motor vehicle traffic gases has been associated with decreased cognitive development [56,57]. Nitrogen dioxide (NO_2) exposure is associated with reduced IQ performance and lack of psychomotor development in young children [58]. Studies suggest that exposure to air pollution during pregnancy causes adverse effects on the cognitive performance of infants. A study found that increasing average NO_2 concentrations were associated with decreased gross motor skills in children [59]. Also, increased nitrogen dioxide levels are associated with reduced memory span among school children aged 9-11 [60]. It has been observed that as environmental levels of black carbon, whose concentration in the air increases as a result of the use of organic fuels, increase, intellectual performance such as visual vocabulary, compound intelligence, visual learning, and memory decrease in children [61,62].

1.9. Heavy Metals

Although some studies have suggested metal transfer to the fetus during pregnancy, the evidence is insufficient for all heavy metals [63]. Cd transfers to the fetüs during pregnancy, but it appears restricted [64]. Exposure to As at an early age affects brain weight and the neurotransmitter system, causing deficits in intelligence and memory [65]. Since Pb does not accumulate in the placenta, the Pb concentration in maternal blood is almost the same as in fetal blood [66]. Methyl mercury (MeHg) causes brain damage in the prenatal period [67,68]. Mn and As are the metals with the highest accumulation rates in the rat brain after a single exposure [69]. Pb and Cd exert synergistic effects to reduce the expression of glial fibrillary acidic protein, an essential macromolecule in the BBB [70,71].

An in vivo study in rats from prenatal to early life found that exposure to As produced an imbalance in the antioxidant defensive mechanism and neurotransmitter metabolism in the hippocampus region of the brain [72]. Here, As it reduces glutathione (GSH), glutathione peroxide (GPx) increases glutathione synthase (GS) activity and lipid peroxidation [73]. ROS and lipid peroxidation elements released due to oxidative stress increase superoxide dismutase (SOD) activity and decrease glutathione-related enzymes, leading to

changes in the cellular redox state [74]. It activates c-Jun N-terminal kinase 3 (JNK3) and p38 mitogen-activated protein kinase (p38 MAPK), which induces apoptotic factors in cerebral neurons. Causes brain cell damage and subsequent death and impairments in neurobehavioral function [75-78].

1.10. Organochlorine pesticides

Organochlorine pesticides (OCPs) have been extensively used, but their use has been reduced due to their environmental persistence and neurotoxic effects [79,80]. They pose a risk due to their excessive bioaccumulation [81]. Prenatal exposure to organochlorine compounds (OCs), among organochlorine pesticides, negatively affects neuropsychological development. In addition, maternal exposure to OCPs causes deterioration in cognitive and motor development and the occurrence of autism in the postnatal period. These environmental agents cause postnatal toxicity in infants not only through in-utero exposure but also through breastfeeding [82-84]. Considering the relationship between PD and exposure to organochlorines, it has been suggested that organochlorines lead to the accumulation of α-synuclein and depletion of dopaminergic neurons, thus predisposing to Parkinsonism [85]. In a study conducted in Finland, hexachlorobenzene (HCB) and dichloro diphenyl dichloroethylene (DDE) were detected in 75 cases of autism among 1.2 million newborns [86,8]. In an intrauterine study in pregnant mice and rats, even a single prenatal exposure to chlordecone was found to cause neurological disorders such as cerebral anomalies, decreased birth weight, stillbirth, tremors, memory impairment, and altered responses to stress [88]. Prenatal exposure to chlordecone has been observed to be associated with impairment in fine motor skills as scored by the BrunetLe'zine Psychomotor Development Scale in Early Childhood [89]. Chlordecone, which has acute and chronic toxic effects, causes neurotoxicity as well as immunotoxicity and reproductive, musculoskeletal, and liver toxicity. It has been suggested that motor dysfunctions and tremors observed in newborns due to chlordecone exposure are modulated by significant signaling pathways such as serotonergic, GABAergic, cholinergic, and dopaminergic systems in striatal neurons located in the basal ganglia and medial pontomedullary reticular formation [90,91]. It has been reported that the risk of autism is increased in children of mothers exposed to organochlorines in the first three months of pregnancy [92]. Prenatal exposure to PCBs and non-dioxin-like PCBs has been documented to increase the risk of impulsive behavior and attention-deficit/hyperactivity disorder [93]. Early exposure of the infant to PCBs through breastfeeding results in an increased prevalence of anxiety behavior with decreased exploratory behavior and locomotor activity [94]. Additionally, Forns et al. reported that exposure to PCBs in utero had adverse effects on cognition and psychomotor development [95]. The most important mechanism underlying the neurotoxicity observed due to PCB exposure is that it causes high sensitivity in the cerebellum, which provides motor control, including motor skills, cognitive development, attention, balance, and coordination [96]. Neurotoxicity is specifically associated with alterations in the cerebellum [97,98]. Disruption of myelination during the neurodevelopment process and changes in the concentrations of some monoamine neurotransmitters have been identified as the most important mechanisms underlying neuropsychological deficits caused by some organochlorine insecticides such as hexachlorobenzene [99].

Epidemiological studies have reported that PCBs show their neurotoxic effects through imbalances in inhibitory and excitatory neurotransmission that cause social, emotional, and cognitive development, language and speech development, and the primary symptoms and seizures of autism. Prenatal exposure to

PCBs and their hydroxylated polychlorinated biphenyls (OH-PCBs) has been found to cause decreases in mental and psychomotor developmental indices [100-103].

1.11. Human Immunodeficiency Virus

Maternal exposure to human immunodeficiency virüs (HIV) during pregnancy can cause impaired neurodevelopment of the child in the first years of life. During pregnancy, a woman's immune system becomes weaker than usual. With the known total immunosuppressive effect of HIV, it is thought that pregnancy may accelerate HIV infection and the development of acquired immune deficiency syndrome (AIDS) [104]. Different hypotheses have been proposed that exposure to HIV may affect pediatric brain development. Exposure of the fetus to inflammation in utero may weaken the developing brain's defenses against adverse postnatal conditions [105,106]. In the presence of HIV infection, chronic inflammation may continue despite antiretroviral therapy. Therefore, immune disorders may occur in pregnant women receiving HIV treatment [107].

1.12. Alcohol

Prenatal alcohol exposure (PAE) causes behavioral disorders and increases the risk of metabolic diseases [108]. Neuroinflammation is believed to contribute to ethanol-induced neurodegeneration; this suggests that anti-inflammatory therapeutics may provide a novel preventive approach for the treatment of fetal alcohol spectrum disorders [109]. Prenatal alcohol exposure also negatively affects the developing anatomical structures of the brain and body, leading to a variety of behavioral, cognitive, and physical effects [110].

1.13. Illicit drugs

Abuse of legal and illegal drugs is a worldwide problem of concern in pregnant women. The effects of illicit drugs depend on the duration of exposure, timing, dose, and degree of distribution of the drug. Teratogenic effects are observed as a result of fetal exposure to illicit substances. Long-term health problems triggered by oxidative stress and epigenetic changes in children of substance-addicted mothers play a role in the pathogenesis of neurodevelopmental disabilities. Disruption of redox homeostasis is an essential factor in the pathogenesis of illicit drug use-induced neurodegeneration, and new treatment alternatives are being investigated to prevent neurodegeneration through antioxidant and epigenetic modulator mechanisms. Important neurodegeneration targets must be identified to develop new neuroprotective strategies [111].

The most widely abused illicit drug during pregnancy is Cannabis sativa (marijuana) [112]. Studies conducted on experimental animals have shown that exposure to marijuana during the developmental period may pave the way for psychiatric diseases in children by affecting the endocannabinoid system in the brain. Endocannabinoids are secreted from postsynaptic neuron membranes in the brain, where cannabinoid receptor type 1 (CB1) receptors are activated; they spread rapidly by binding to the presynaptic neuron membrane from behind [113].

Additionally, exposure to the active ingredient in marijuana (T1-9-tetrahydrocannabinol/THC) in utero may alter responses in the mesolimbic dopamine pathway, leading to changes in the inhibitory and excitatory effects of dopamine on neurons [114]. As observed with many neurotoxic agents, the severity and

persistence of the impact of exposure to illicit drugs on the fetus's brain depend on the type of opioid, time of exposure, and dose. The opioids whose prenatal exposure has been most studied include methadone, morphine, oxycodone, and buprenorphine [115].

In utero, exposure to different types of opioids has been examined in studies in rat models. For example, buprenorphine and methadone cause changes in myelination and axon length, while morphine causes an increase in spine density and dendritic length [116].

Opioids show their effects by binding to opioid receptors in the brain and spinal cord, such as mu, delta, and kappa. The binding of opioids to these receptors prevents the release of neurotransmitters released by presynaptic neurons. Long-term use of opioids can lead to increased neuroinflammation. This can accelerate the progression of neurodegenerative diseases such as Alzheimer's disease. Some studies show that opioids can block neuroprotective mechanisms in the brain, which can negatively affect the course of diseases such as Alzheimer's disease. The effect of opioids on the dopamine system can improve some motor dysfunctions in Parkinson's patients. It has been shown that opioids can affect plasticity in the brain, changing the ability of neurons to connect and learn [117].

Methamphetamine is one of the most frequently used illegal drugs, like marijuana, heroin, and cocaine. Although factors such as the content of the substance used and the duration of use may vary in the findings observed in the newborn, all babies of mothers who use substances should be closely monitored for neonatal abstinence syndrome for 72-96 hours, and it should be taken into consideration that the findings may last longer. Generally, babies who develop neonatal abstinence syndrome are neurological (agitation, hyperactivity, increased muscle tone, tremor, jitteriness, myoclonic beats, high-pitched cry, hypotonia, sleep disorder, apnea, seizure), gastrointestinal (decrease in sucking, hyperphagia, vomiting, diarrhea), vasomotor symptoms such as sweating, hypothermia, and fever may be observed. Although these effects of methamphetamine are well known, its effects in early infancy and its long-term effects are not fully known. The most common recorded impacts in newborns include growth retardation, change in height and head circumference, and low birth weight [118,119].

Following prenatal exposure, amphetamine has been detected in the human umbilical cord tissue, plasma, and placenta during the first trimester. The cellular effects of amphetamine are nearly identical to methamphetamine, including increased levels of norepinephrine, dopamine, and 5-HT in the synaptic cleft through transporter reuptake inhibition. Using amphetamines during pregnancy also increases the risk of adverse effects such as placental bleeding [120]. Amphetamine negatively affects fetal brain growth and also reduces the amount of blood reaching the placenta by vasoconstriction. Depending on this situation, the embryo may not receive enough nutrients [121]. It has been observed that children exposed to amphetamines during the prenatal period are one year behind their peers in school success at the age of 14-15 [122].

In a study, delays in the motor skills of babies were observed up to two years after prenatal 3,4-methylenedioxymethamphetamine (MDMA), also called ecstasy exposure [123]. Behavioral studies conducted in animals have found significant adverse effects on learning, motor skills, and memory tests following exposure to MDMA. Although there was a decrease in motor activity and impairment in memory

and neuronal development in the offspring of rats exposed to prenatal MDMA and alcohol, it was not determined whether these effects were due only to MDMA [124].

1.14. Smoking

Smoking and exposure to nicotine during pregnancy have been associated with miscarriage, premature birth, sudden infant death syndrome, stillbirth, perinatal morbidity, and low birth weight. Recent data from clinical and preclinical studies suggest that exposure to nicotine during pregnancy may alter babies' brain circuits and responses, as well as increase the risk of adverse neurodevelopmental disabilities such as depression, anxiety, and attention deficit hyperactivity [125,126]. Some preclinical and clinical research focuses on neurodevelopmental and neurobehavioral complications. Nicotine binds to neuronal nicotinic acetylcholine receptors (nAChRs), which mediate rapid neurotransmission in the central and peripheral nervous system [127].

1.15. Diet

Mother's nutritional status and diet play an essential role in the neural development of the offspring. Changes in these early-life feeding schedules may have long-term effects on offspring health. A maternal diet rich in essential vitamins and nutrients significantly prevents various diseases, including stroke [128]. A study of the impact of maternal single-carbon diet deficiencies during pregnancy and lactation and their effects on stroke outcomes in offspring later in life found that maternal folic acid or choline deficiencies have a significant impact on ischemic damage, neurodegeneration, and neuroinflammation [129]. Prenatal nutritional deficiencies have detrimental effects on brain structure and functioning. Prenatal malnutrition has been associated with poor cognitive performance [130]. Gender-specific effects of malnutrition on brain volumes during early pregnancy have been reported. Study results show that malnutrition causes smaller brain volume in later life in men compared to women [131]. Therefore, the influence of the prenatal fetal environment on brain structure and cognitive functions may continue not only in early childhood but also throughout life. However, studies on the long-term neurological consequences of prenatal harmful factors later in life are limited.

1.16. Future Directions and Clinical Implications

Although neurogenetic disorders occur in the prenatal period, they can also happen in the future as widespread and early-onset brain damage. Examples include acute infantile neuronopathic disease (Gaucher type II) and mucopolysaccharidoses. Postpartum enzyme replacement therapy cannot be used widely due to BBB and neuron damage [132]. Effective and safe gene therapies are needed that can prevent early-onset neuropathy, correct the mutation, and protect the developing brain [133]. Neurodegeneration due to prenatal exposure to neurodegenerative agents is ideally treated in utero. A single dose of AAV1-HβH, which transduces human β-glucuronidase (GUSB), was effective in a mouse model. This lysosomal storage disease causes the spinal cord and brain degeneration, intellectual disability, skeletal abnormalities, and growth retardation [134]. One study found that prenatal and early postnatal treatment of pregnant mice with P021, a neurotrophic compound synthesized for the first time, reduced cognitive deficit and abnormal hyperphosphorylation, tau accumulation, and amyloid-β plaques. P021 competitively inhibits the leukemia inhibitory factor and increases brain-derived neurotrophic factor transcription, neuronal proliferation, and

differentiation. Oral administration of the compound increases neuronal plasticity and neurogenesis in rats [135].

Fetal gene therapy for inherited genetic diseases offers a prophylaxis option, especially against irreversible and fatal pathological changes. The acute childhood fatal form of neuronopathic Gaucher disease is not treatable. Because the enzyme cannot cross the BBB, these patients exhibit symptoms associated with hindbrain neurodegeneration, such as strabismus, neck hyperextension, and fatal apnea. After intravenous and intracerebroventricular injection of glucocerebrosidase (GCase), Gaucher cell infiltration was inhibited. As a result, it can be said that intracerebroventricular gene therapy may effectively treat fatal neuropathologies [136].

The presence of inflammation during fetal development and the fetus being affected by this inflammation increases the risk of neurological disorders in later life. Prenatal exposure to inflammation also affects the etiology of age-related neurodegenerative diseases. Gestational inflammation during pregnancy disrupts the formation of the fetal BBB through a cyclooxygenase-2 (COX2)-dependent mechanism. These functional and structural changes in the BBB, which continue after birth until later life, lead to excessive permeability. It has been suggested that microglia in the fetal brain's perivascular area increase due to COX2 activity [137].

HIV infection is known to be transmitted from mother to baby. Practical approaches to reducing perinatal transmission include mono/combined antiretroviral therapy applied to the mother or the baby, preferring cesarean delivery, and especially HIV-positive mothers not breastfeeding their babies. Among the theoretically practical approaches, washing the birth canal with disinfectants (5% chlorhexidine), avoiding artificial opening of the membrane, using immune therapy, and supplementing the mother with vitamin A can be listed. Antiretroviral drugs are not widely used, especially in developing countries, due to reasons such as the cost of antiretroviral treatment and the side effects of the drug. Requiring HIV tests from pregnant women, advising mothers not to breastfeed their babies, and testing drugs on experimental groups are approaches to reduce and prevent the transmission of HIV from mother to baby in health care [138].

Effective and implementable clinical approaches to protect prenatal neurological development and prevent neurodegenerative diseases can reduce the risk level. Early detection of exposure to environmental toxins during pregnancy may be critical to protecting fetal neurological development. Prenatal screening can be conducted more comprehensively to identify risks to pregnant women exposed to agents such as heavy metals, pesticides, and endocrine disruptors. These screenings can enable closer monitoring of high-risk groups and appropriate measures to be taken. Public health policies can be developed to reduce the effects of environmental factors on neurodegeneration. In particular, regulations can be introduced to minimize pregnant women's exposure to toxic chemicals, air pollution, and harmful industrial emissions. In addition, more investment should be made in public health research to understand the long-term consequences of harmful environmental exposures. More education and awareness should be created about environmental factors during pregnancy and the potential effects of these factors on the fetus. Pregnant women, family members and health professionals should be made more aware of environmental agents. In the future, educational campaigns can be organized at all levels of society about the effects of environmental exposures on neurological development. The interaction of genetic and environmental factors in the prenatal period should be investigated in more detail. Examining the effects of environmental toxins, especially in

individuals with genetic predisposition, observing this interaction and determining individual risk factors will provide important information for future treatment and prevention strategies for neurodegenerative diseases. Understanding the molecular mechanisms of prenatal neurodegeneration will contribute to the discovery of new therapeutic targets. These discoveries may guide the development of treatment methods that can stop or delay the neurodegeneration process.

1.17.Policies and Public Health Measures Implemented to Reduce Environmental Exposures

Air pollution is one of the factors that cause harmful effects on the neurological development of the fetus during pregnancy. Stricter emission control laws and regulations limiting industrial emissions can be implemented to improve air quality. These policies will reduce the effects of environmental toxins on the fetus and directly reduce the prevalence of neurological diseases. Strengthening laws against environmental toxins such as industrial chemicals and pesticides can significantly reduce the risk of exposure to these substances during pregnancy. Public health measures targeting pregnant women in particular will be an important step in reducing environmental exposure. Regulations aimed at reducing air and water pollution can help prevent the spread of many diseases, such as neurological diseases, by reducing the chemicals that will be exposed to the environment. Early detection of exposure to environmental toxins is important, especially for women in high-risk groups. Prenatal screening can help identify women exposed to toxic substances and take steps to reduce the risks. Early screening and monitoring can prevent possible adverse effects on fetal development by protecting pregnant women at high risk from environmental toxins. This can be effective in preventing neurological diseases by directly protecting brain development. Education programs can be organized to raise public awareness about environmental exposures during pregnancy and their negative effects on the fetus. Pregnant women can be guided to avoid exposure to toxins in particular. Such awareness studies will enable the public to become more aware of environmental risks and can take personal protective measures. Environmentally friendly agriculture and production methods should be encouraged, and organic farming practices should be expanded. Policies encouraging organic farming practices can be implemented to reduce the harms of pesticides and other chemicals used in agricultural production. By using environmental exposure monitoring systems, it becomes possible to monitor environmental toxins to which pregnant women are exposed and to determine exposure in advance. At the very least, the risk potential in risky areas can be determined and early warning can be provided. Systematic monitoring of exposure allows measures to be taken to protect public health. Understanding prenatal neurodegeneration at the molecular level can lead to the discovery of new treatment targets. Access to health services should be increased, and better access to health services should be provided in low-income and high-risk communities. Regular health checks for pregnant women can offer information and support regarding protection from environmental exposures**.**

2. CONCLUSION

Adverse prenatal exposures to the fetus are associated with changes in brain development later in life. The fetus is exposed to alcohol, addictive substances, and drugs in the womb. Exposure to cocaine, opioids, pathologies associated with placental dysfunction, nutritional deficiencies, and chronic diseases such as maternal anemia cause a decrease in brain size and changes in the temporal lobe and hippocampal volumes. The reduction in brain reserve paves the way for an increase in the risk of dementia. In addition to the acute adverse effects that develop due to fetal exposure to drugs of abuse and illicit substances during pregnancy,

it also causes permanent changes in brain function and structure. Additionally, the molecular targets of psychoactive drugs may be different in infants and children than in adults. Psychoactive drugs with synaptic modulatory roles in adults may have very different effects during early development. Surprisingly, research in this area is still in its infancy, and more precise and mechanistic studies are needed to characterize the extent of neurobehavioral changes. Its socioeconomic impact is also significant, given the costs of private education, long-term medical management, and lifetime loss of productivity.

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Author's Contribution

SS: writing, conceptualization, review, editing, and visualization; SÜ: writing – review and editing.

The Declaration of Ethics Committee Approval

This study does not require ethics committee permission or any special permission.

Declaration of research and publication ethics

The authors of the paper declare that we followed the scientific, ethical and citation rules of Environmental Toxicology and Ecology in all processes of the paper and that we did not make any falsification of the data collected. Furthermore, we declare that ETOXEC and its Editorial Board are not responsible for any ethical violations that may have occurred and that this study has not been evaluated in any other academic publication environment than ETOXEC.

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