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Review Article

Toxic Metals Exposure and APOE4 Gene Variant in Cognitive Decline Disorders

Gasmi, A[1 *], Menzel, A[2], Piscopo, S[1, 3], Noor, S[4]

1. Société Francophone de Nutrithérapie et de Nutrigénétique Appliquée, Villeurbanne, France
2. Laboratoires Réunis, Junglinster, Luxembourg
3. Research and Development Department, Nutri-Logics SA, Weiswampach, Luxembourg
4. Institute of Molecular Biology and Biotechnology, Bahauddin Zakariya University Multan, Pakistan

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Corresponding Author: dr.amin.gasmi@gmail.com

Abstract

Neurodegenerative disorders are those which affect cognitive functions. Misfolding of proteins especially apolipoprotein E is a key genetic factor involved in several cognitive impairments. Increasing evidence also described the toxic effects of metals, generated by both nature and humans, on the development of neurological disorders. Understanding of interaction between toxic metals and apolipoprotein E protein in cognitive decline diosrders would provide alternative treatment options. Google Scholar and PubMed database were used to search the articles using different search terms like 'toxic metals', 'cognitive decline', 'Apolipoprotein E', "neurodegenerative disorders" and "metals neurotoxicity". Only those papers were included that discussed the metal exposure-apolipoprotein association in the development of cognitive decline disorders. Heavy metals are particularly recognized as a major source of neurotoxicity. These toxic metals can interact with genetic factors and play important role in disease etiology. Understanding the underlying mechanism of this interaction could provide tremendous benefits to treat cognitive decline disorders. In this study, the role of the apolipoprotein E4 gene in the development of cognitive disease conditions and their phenotypes has been discussed thoroughly which leads to the accumulation of amyloid-beta fibrils. This exploratory study revealed novel hypothetical findings which might contribute to the understanding of the neurotoxic effects of chronic toxic metals exposure and possibly improve our knowledge on the molecular mechanisms linking metal exposure to cognitive decline disorder risk.

Keywords: Toxic Metals, Brain, Apolipoprotein E, Neurodegenerative disorders, Alzheimer's disease

1. Context

Neurodegenerative disorders are associated with neurodegeneration and loss of neuron functions, ultimately results in progressive cognitive decline. Misfolding and clustering of specific proteins either in or outside of cells are common histopathological characteristic features of neurodegenerative disorders. For example, aggregation and misfolding of alpha (α) synuclein protein in the form of Lewy bodies occurs in nerve cells that leads to the development of Parkinson's disease (PD). Accumulation of amyloid-(A) protein and formation of neurofibrillary tangles from hyperphosphorylated tau cause Alzheimer's disease (AD). Two other neurodegenerative disorders i.e., Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) are caused by mutation in the huntingtin (HTT) gene and TAR DNA-binding protein 43 (TDP-43), respectively. Among all cognitive disorders, the two most prevalent disorders are AD and PD (1).

AD is a progressive neurological disease that causes rapid cognitive impairment and loss of memory with

age, having a huge impact on public health. Most of the AD cases are infrequent or irregular and develop later in life. Even though the underlying cause of late-onset AD is unknown, an interplay of genetic and environmental risk factors is perhaps most likely to be responsible (2). The interaction between genetic predisposition and environmental factors may cause cognitive decline to become even more serious and accelerated. However, there is a scarcity of evidence to back up this claim (3).

Apolipoprotein E (ApoE) is a type of protein that is synthesized mostly by astrocytes, and it facilitates the transport of cholesterol to neurons. This transportation of cholesterol towards neurons is mediated by the binding of ApoE with the low-density lipoprotein (LDL) receptor family of proteins. ApoE acts as a ligand for LDL receptors. This process is necessary for axon development, synapse formation, and remodeling, along with all of the necessary events for learning, memory, and neural regeneration (4). Decreased levels of ApoE protein and LDL receptor causes the dysfunctional synaptic repairment and gradual loss of synapses in the cortex and hippocampus regions of the brain (5). ApoE is a polymorphic protein, and it has three different allele variants including ApoE2, ApoE3, and ApoE4. The ApoE gene variant ε4 is the most well-known genetic risk factor of delayed, sporadic AD, and this variant is responsible for 99% of cases of AD. 2 single nucleotide polymorphisms (SNPs) in the ApoE gene control the type of amino acid will place at 112 and 158 positions at the protein level. ApoE2 variants comprise Cys112 and Cys158, ApoE3 variant contains Cys112 and Arg158, and ApoE4 variant contains Arg112 and Arg158 amino acids. ApoE4 heterozygotes have a five times higher chance of developing AD, whereas ApoE4 homozygotes show a 20 times higher risk. ApoE2 is believed to have a protective role against AD (6).

Association has been found between metals and the ApoE gene in the case of AD. Metal ions may interact with ApoE in three different ways, according to Xu and colleagues. One mechanism could be the accumulation of copper (Cu), zinc (Zn), and iron (Fe) in amyloid plaques (AP). AP plaques prompt metal dyshomeostasis, which results in a decreased ApoE levels in AD. The second mechanism may involve the reduction in ApoE transcription and translation due to metal dyshomeostasis. As ApoE promotes the clearance of amyloid-(A), decreased levels of ApoE protein produce amyloid toxicity in AD. Thirdly, ApoE4 isoforms are more affected by ApoE proteolysis in AD, which disrupts mitochondrial and cytoskeletal processes, resulting in neurodegeneration (7). Metal-binding may have a role in ApoE isoform stability, and because metals stabilize isoforms of ApoE in ε2 > ε3 > ε4 order, this might explain why the ApoE4 isoform is more susceptible to proteolytic degradation. These assumptions, however, need to be verified more extensively (7). Therefore, these pieces of evidence point out that harboring the ApoE4 polymorphism alone is not enough to cause cognitive decline disorders, revealing that other risk factors must interact with ApoE4 to increase the risk of developing cognitive decline disorders (8).

Breathing in polluted air, cutaneous penetration of metals found in soil, and consumption of contaminated water and food are all routes through which humans continuously get exposed to toxic metals. The modern lifestyle has considerably increased the levels of toxic metals in the environment. Lead (Pb) and Cadmium (Cd) are two naturally present metals that are extensively utilized for a multitude of applications, including industrial and household. Their uses can also be found in agricultural applications. As a consequence, the environment now has a worldwide dispersion. Pb and Cd can cause multiple organ damage even at low exposure levels, posing a serious health risk to humans. The International Agency for Research on Cancer has categorized Cd as a human carcinogen and Pb as potentially carcinogenic to humans (9). A growing body of available data has emerged that indicating the Pb and Cd toxicity also targets the central nervous system (CNS), inducing cognitive implications and that both Pb and Cd contamination are potential causative

determinants for sporadic AD, in addition to their carcinogenic potential. Pb, and perhaps also Cd exposure can cause AD-like pathologies such as memory impairment and intellectual ability problems, focus, language, and emotional deficits, according to a population-based study (10, 11). Several other metals such as aluminum (Al), arsenic (As), and Manganese (Mn) is also posing serious threats to human health especially damaging brain health (12).

This study summarizes the understanding of metals association with ApoE variants as this connection plays important role in the etiology of several cognitive decline diseases. Understanding this underlying mechanism of metal-ApoE variants will help researchers to formulate future research to devise new and more precise treatment approaches for cognitive decline disorders.

2. Evidence Acquisition

The main purpose of this article is to highlight the interaction between different metals like cadmium, lead, mercury and arsenic with APOE gene and its variants. For data retrieval different keywords were used to gather relevant information using two widely used databases, i.e., Google Scholar and PubMed. Keywords used to search the relevant studies were, 'toxic metals', 'cognitive decline', 'Apolipoprotein E', "neurodegenerative disorders" and "metals neurotoxicity", "ApoE variants and toxic metals", "ApoE variants and neurodegenerative disorders" etc.

The inclusion criteria was set that only peer reviewed articles about toxic metals exposure and APOE4 gene variant in cognitive decline disorders were included in this review. Other than the direct search, cross referencing was also employed from the already reviewed and included studies to broaden the search of more relevant articles. Only published studies were included in this review, and all other articles and studies were excluded. Data was collected in almost 1 month. Figure 1 shows the flowchart diagram of number of articles obtained from different databases and selected for this review.

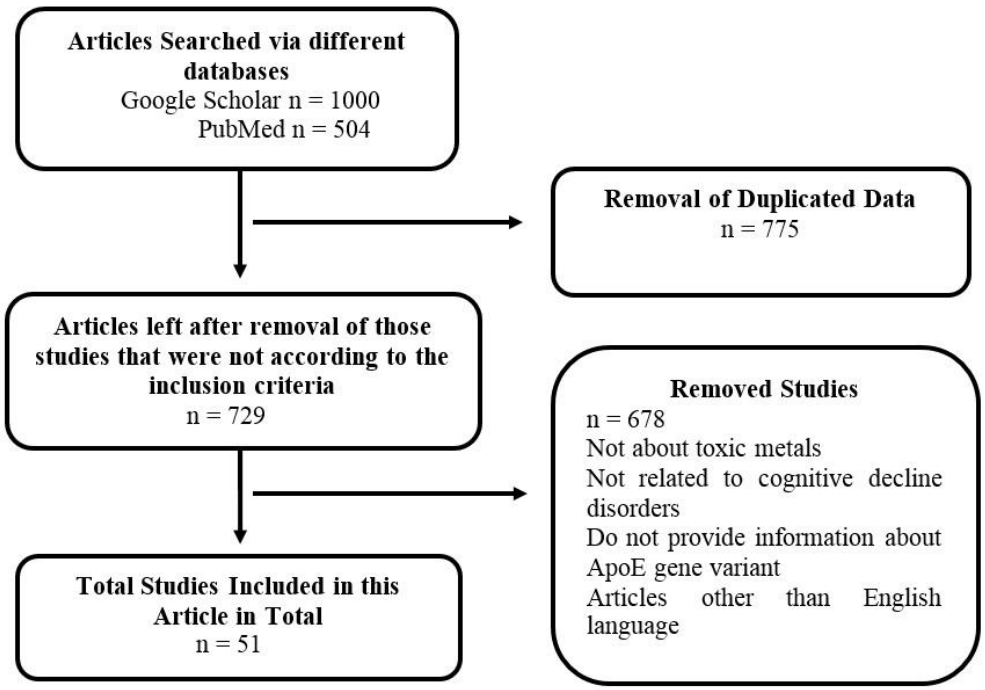

Figure 1. Summary of the searched information, and the method selected for data collection

3. Results

3.1. Toxic Metals as a Risk Factor for Cognitive Decline Disorders

Even though most genomic studies have focused on the relevance of SNPs and de novo mutations in the development of cognitive decline disorders, environmental exposure has also been associated with disease pathogenesis. Neurodegenerative disorders can be influenced and triggered by a wide range of environmental factors. According to the Global Burden of Disease Study, the prevalence of the disease caused by environmental pollution has now become a public health concern globally, with 6.4 million fatalities attributed to air pollution in 2015 (13). Environmental exposure along with the interaction of genes and environment has a strong influence on the onset and development of AD and PD, according to experimental and epidemiologic evidence. Toxic metals, insecticides, surfactants, solvents, and also other commercial by-products are all toxins that can cause cognitive problems. These toxins can intercept the BBB, presenting a hazard to public health and the efficiency of brain cells (14).

Due to the endurance and bioaccessibility in the atmosphere, heavy metal ions are regarded as the worst health hazard to humans, out of all types of pollutants. Toxic metals have become more common as a result of growing industrialization. Cognitive impairments have been related to long-term exposure to transition metals including Mn, Fe, Cu, and Zn. Disease-related proteins such as Aβ, tau, and α-synuclein go through conformational changes that are crucial in the pathogenesis of neurological disorders (15). The oligomerization of Aβ and its conformational modifications are essential for the Aβ-induced neurodegenerative mechanism. Amyloid fibrils are insoluble aggregates formed by Aβ oligomers. Factors that expedite oligomerization may have a profound impact on AD pathogenesis. Some accelerating factors involved in modification of proteins confirmation are trace elements including Al^{3+}, Zn^{2+}, Cu^{2+}, Mn^{2+}, and Fe^{2+}, which can facilitate Aβ oligomerization (16). According to a recent study, Mn2+ exposure can increase the risk of cognitive decline disorders (17). Mn^{2+} stimulates a higher level of α-synuclein secretion and serves as a major NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome signaling accelerator. Mn^{2+} can crosses the BBB all alone or in conjunction with transferrin or citrate (17).

Al is a trivalent metal neurotoxin that has been linked to neurodegenerative disorder's pathogenesis. Al^{3+} penetrates the CNS by a similar route as Fe^{2+}. Accumulation of Al^{3+} in the CNS triggers pro-inflammatory signaling, permanent brain cell damage, gene expression dysregulation, and dysfunctional cognitive, memory, and behavioral actions (18). Inflammatory neurodegeneration, which includes amyloidogenesis, inflammasome increased expression, abnormalities in neurotrophic signaling and synaptogenesis, modified innate immunity, generation of reactive oxygen species (ROS) and α-synuclein, and the failure to clear self-aggregating waste from brain cells, cytoplasm, and parenchyma, are the mechanisms of Al^{3+} toxic effect (19). The imbalance of Zn^{2+} and Cu^{2+} is critical for the pathophysiology of AD and PD. Excess intracellular Zn is released from metallothioneins due to aggregation of Aβ aggregation and ROS generation, which may disrupt mitochondrial function and cause apoptosis. Increased levels of Cu^{2+} are considered neurotoxic, and its neurotoxicity has long been attributed to its high affinity for Aβ and stimulation of higher oxidative stress through the Fenton reaction (20). Pb, As, and methyl mercury (MeHg) have all been found to act as toxins that can interrupt cognitive function, induce neurological problems, and accelerate the risk of AD and PD by impairing mRNA splicing, the ubiquitin-proteasome system, the electron transport chain, and oxidative stress, as described by several studies (21, 22).

3.2. Toxic Metals Exposure and APOE4 Gene in Cognitive Decline Diseases

ApoE seems to have a critical role in neurodegenerative disorders, according to several studies. Roses, who found polymorphic variants of

ApoE genes, uncovered the mechanism of this gene involvement in cognitive disorders. As a result, it is possible to treat these cognitive disorders simply by turning on or off the ApoE gene, which will change the ApoE protein, and result in positive outcomes if we upstream the protective role of this gene or allele on chromosome 19 (23). As ApoE could serve as a binding site for different metals, the association of metals and ApoE is crucial for the etiology of cognitive decline diseases (24). Investigation of this metal-gene association would be a great breakthrough in the study of cognitive decline disorders.

3.2.1. Cadmium (Cd)

Cd is a harmful heavy metal that is emitted into the atmosphere by both natural and anthropogenic causes, and it is accumulating in plants such as green vegetables, rice, and tobacco. As a result, the two most common causes of Cd exposure in the general population are food intake and tobacco smoking (25).

Persistent exposure to Cd for a long time in humans can damage multiple organs, such as the kidneys, liver, and bones, and some studies have suggested that Cd is also a neurotoxin. Cd has been found to cause cell death in several neuronal cells including primary neural stem or progenitor cells in in vitro experiments (26, 27). Cd causes serious hemorrhages in the cerebral cortex and cerebellum, disrupts neurotransmitter functioning, and disrupts passive avoidance, schedule regulated response, and conditioned inhibition, according to several animal studies (27, 28). However, the entire range of Cd's neurological effects has yet to be discovered. Cd may cross the BBB and deposit in the brain, inducing neurotoxicity by triggering signaling pathways linked with inflammation, oxidative stress, and neuronal death, along with other events (27). A link between Cd exposure and cognitive impairment in humans has been indicated by several epidemiological research studies (26, 29). In male C57BL/6 mice, a recent research study (26) found a strong causal link of Cd exposure with cognitive impairments. The effects of 3 mg/l $CdCl_2$ on hippocampus-dependent and short-term olfactory memory were revealed in this investigation (26). Based on these findings, it can be anticipated that interaction of gene and environment between ApoE and Cd exposure might worsen the cognitive decline in ApoE4 allele carriers in comparison to ApoE3 allele carriers. In a recent study (30), the researchers used mice models of AD that had an active form of the ApoE gene's E4 or E3 variant. The investigators subsequently introduced low doses of Cd to the mice's drinking water, which they drank for 14 weeks. The highest quantity of Cd that the mice ingested was equal to the amount of Cd that people in the United States, including those who have never smoked, had in their bloodstream. The rats' cognitive skills were tested using standard novel objection location tests and T-maze tests. The researchers selected to emphasize on cognitive abilities that depend on the hippocampus, a brain region important for learning and remembering. It's also one of the areas of the brain that experiences the most damage in the early stages of AD. The mice that received Cd did not perform well in the novel object location tests, suggesting that their short-term spatial working memory was impaired. These symptoms appeared earlier in mice carrying the ApoE4 gene as compared to those mice carrying the ApoE3 gene. Male mice with the same genetic profile developed the disease earlier as compared to female mice with the similar genetic profile. This study concluded that the Cd exposure disrupt neuronal development of adult-born nerve cells in the hippocampus of male mice with the ApoE4 gene. Collectively, the findings shows that an interplay between ApoE4 and Cd exposure results in accelerated cognitive decline, with decreased adult hippocampus neurogenesis being one of the underlying mechanisms. In general, young male mice found to be more prone to the effects of this interplay as compared to young female mice. This study provides direct evidence for an interaction between this AD genetic risk gene and environmental exposures on increased cognitive

impairment. The researchers have also discusses several processes that might explain the fact p that ApoE4 causes BBB leakage, resulting in increased Cd deposits in the ApoE4 brain (30).

3.2.2. Lead (Pb)

Plumbum (Pb), often referred to as lead, is a heavy metal and a chemical element belonging to the carbon family. Though Pb poisoning has been documented over decades, in 1892 it was regarded as a major risk to health after a study revealed that white lead paint on terraces and railings in Brisbane, Australia, caused chronic neurological problems in children (12). The half-life of ambient Pb absorbed into the blood is 30 days. Pd adheres to circulatory erythrocytes and circulates through the body, eventually accumulate in bone.

Pb is transported throughout the body after it enters the bloodstream, making it more accessible to different tissues of the body (12). Pb substitutes for Ca ions in brain vessels, allowing it to quickly pass the BBB. Pb levels in the brain disrupt neurodevelopment and induce serious brain damage. Even low concentrations of Pb have been found to stimulate neurotransmitter changes, perhaps leading to GABAergic, dopaminergic, and cholinergic system dysfunction. Pb substitutes Ca and other important metals within cells, disrupting biometal-dependent processes in this way (12, 31). In vivo and in vitro studies indicated that Pb exposure was linked to higher amounts of Aβ peptides (32, 33). Higher Pb levels were also found to be associated with increased amyloid precursor protein (APP) expression as well as increased Aβ peptide synthesis in rats (34). Pb toxicity in childhood has been linked to neurofibrillary tangles in the brain, according to a case study (35). A research study comprising of 55 young adults, who had participated in a prospective cohort study as newborn babies, found inverse correlations between umbilical cord Pb levels and expression of possible AD genetic markers such as ADAM9 (A disintegrin and a metalloprotease 9), RTN4 (Reticulon 4), and LRPAP1 (LDL Receptor related protein-associated protein 1) genes, illustrating the effects of early-life Pb exposure on biological processes associated with AD pathogenesis (36).

In the case of Pd, causes that facilitate permanent damage to brain cells and the CNS, give pathophysiological responses. And in this way, some pathological signals have been examined that produce short and long-term effects on BBB and other CNS parts (37). Both animal and epidemiological studies have reported an association between Pd exposures and accelerated cognitive decline and/or AD-associated neuropathology in adults. Interestingly, among workers occupationally exposed to Pd, those with at least one ApoE4 allele experienced accelerated cognitive decline relative to ApoE4 non-carriers. In other research, these data suggest an interaction between ApoE4 having a binding site for lead, exposure leads to faster cognitive impairments. Moreover, disruption of adult hippocampal neurogenesis may cause cognitive behavior deficits, accelerate cognitive decline, and increase AD risk. ApoE is expressed in adult neural precursor cells in the DG and *in vivo* studies using ApoE4-KI mice found that ApoE4 is associated with changes in adult-born neuron survival and maturation in an age- and sex-dependent manner (38). Another study (39) found the association between Pd and ApoE in the development of cognitive decline disorders. The result of this study suggests that people having both ε4 alleles are more prone to Pd effects on the worldwide cognitive decline during aging.

3.2.3. Mercury (Hg)

For centuries mercury (Hg) has remained a major source of toxicity for humans. Major sources are coal stations, waste incinerators, and mining sites. World health organization (WHO) has classified Hg into various types some of which are elemental, organic, and inorganic Hg. Inorganic reservoirs include air, water, skin creams, and toothpaste powder (40). Elemental Hg comes from tooth fillings and industrial wastes. Mainly, inhalation or respiration is the primary source of Hg intake when compared with the inorganic source of Hg that causes poor absorption in the gastrointestinal tract of humans. At the elemental level,

Hg is inhaled in the form of vapors and that can cross the CNS. Methylmercury (organic form) is a major source of contamination as it accumulates in the human biotic environment (41). Most neurotoxic effects of Hg have been found in the brain of the fetus and mother during pregnancy. A recent report has suggested the association of Hg and ADHD (attention deficit hyperactivity disorder**)** in school-age children and presented the reduced learning and writing abilities (42). Moreover, it has more symptomatic consequences in males as compared to females because of differences in endocrine functions. There is a very close relationship between Hg toxicity and autism having similar physical and brain damage symptoms such as overdevelopment, an increase in inflammation, lipid metabolism, necrosis, methylation, etc (43). A high level of Hg has been shown in children having autism disorder resulting in a condition where it accumulates in the body of children of the sample group as compared to the control group (44).

Several evidence has been presented to support the mechanism of Hg toxicity triggered due to oxidative stress resulting in the production of ROS. MeHg accumulates in human red blood cells to a large extent and in a relatively smaller amount in microglial cells (45). An increase in the number of reactive species such as superoxides, peroxides, and oxides causes the peroxidation of lipid molecules. ApoE is the only apolipoprotein that has been associated with the toxic effects of Hg exposure. No other apolipoprotein gene has been associated with the susceptibility to Hg toxicity. Interestingly, the association between ApoE isoforms and the delayed organ damage caused by Hg exposure in humans has been already demonstrated in epidemiological studies. ApoE4 individuals (genotypes: *epsilon 3*/*epsilon 4* and *epsilon 4*/*epsilon 4*) exposed to Hg would have ApoE with decreased ability to bind or chelate the metal compared to individuals presenting the ApoE2 or ApoE3 isoforms. This phenomenon may facilitate the presence of the free form of the metal, allowing it to remain available and exert its toxic effects. This biochemical explanation was proposed based on the differences in the amino acid composition of the three isoforms of ApoE and the affinity of Hg for the sulfhydryl groups of proteins (46).

3.2.4. Arsenic (As)

It is not a metal but a metalloid that exists in both forms whether organic and inorganic in nature. The most common source of As is human activities that involve burning, coal sites, and waste incarnation. The most common source of metals is drinking water and soil that ultimately becomes part of the human diet in turn. Inorganic As that is particularly known for its neurotoxicity gives a better indication for metal exposure and has been studied greatly in literature for its harmful effects. In the brain, stress stimulates oxidative damage that ultimately causes the production of ROS. ROS forms the main pillars of the pathway which is involved in autism and other learning and behavioral abnormalities (47). In children of 10 to 15 years, As exposure is most likely to cause loss of memory and reduced the ability to score IQ tests effectively (48). But up to date, the accumulation of As has not been shown as a cause of change in behavioral activities such as mood. Research conducted on school-going students came forward with a fact that no synergistic effect of Mn and As is found in children having low intelligence problems or who were unable to read and write effectively. Recently, a research was conducted by WHO on a number of students that have some psychological and CNS problems. This study suggested a close and linear i.e., a direct relationship between patients under the age of nine-year and exposure to these toxic metals. Not only this, but it has also found differences in the case of gender i.e., boys with increased hormonal levels were more affected as compared to girls (49). It is also a huge fact that a human being on average gets exposed to various chemicals during life course hence if we put our all efforts into the investigation of one chemical group then it would not give fruitful results or may give false-positive results (50). As treatment does

not modulate endothelial cell-mediated lipid oxidation or smooth muscle cell proliferation but when combined with the ApoE4 gene, it induced the expression of genes coding inflammatory mediators, including interleukin-8. Induction of endothelial inflammatory activity may play a role in As-related vascular effects. In comparison, several studies have suggested that exposure of As associated with APOE4 in very low concentrations such as in parts per billions range will result in sex-specific neurotoxic effects. Males have shown more toxic As form in their urine as compared to females leading to learning and behavioral instabilities in males of all ages either children or young ones. Moderate binding of the APOE4 gene to As presented more harmful effects than that of high-affinity binding leading to intellectual inabilities in patients (51).

4. Conclusion

The review gathers evidence supporting the role of different toxic metals and ApoE alleles in the development and modulation of the cognitive decline disorder. Over the last few decades, the interest of scientists has been shifted towards the brain-related disorders and effects of toxic metals on cognitive decline disorders. ApoE gene and its variants are key genetic risk factors for the development of cognitive disorders. In this context, a large body of research was attributed to study the association of these genetic factors and toxic metals. Evidence from the literature review has indicated that toxic metals bind to ApoE and ApoE facilitates the homeostasis of metals in the brain. Metals may potentially have a role in regulating ApoE levels. The latest studies reviewed in this study increase our awareness of the genetic and environmental risk factors of cognitive decline disorders and help researchers to formulate future research to devise new and more precise treatment approaches for cognitive decline disorders.

Authors' Contribution

Study concept and design: A. G.
Acquisition of data: A. M.
Analysis and interpretation of data: S. P.
Drafting of the manuscript: S. N.
Critical revision of the manuscript for important intellectual content: A. G.
Administrative, technical, and material support: A. G.

Conflict of Interest

The authors declare that they have no conflict of interest.

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