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Review Article

Toxic Metal –Mediated Neurodegradation: A Focus on Glutathione and GST Gene Variants

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Abstract

Increasing pieces of evidence have supported those chemicals from industrial, agricultural wastes and organoleptic activities play important role in the development of neurological disorders. The frequency of neurological disorders is increased to a much extent in recent years with the advancements in science and technology. Google Scholar, PubMed, and Scopus databases were selected to search the relevant information by using keywords including "Heavy metals", "Neurotoxicity", "Glutathione", "Glutathione AND Neurodegenerative disorders" etc. Heavy metals are particularly recognized as a major resource of toxicities during the stage of early pregnancy where a fetus gets exposed to them from maternal activities and circulation. As infants have a weak immune system and cannot respond to the specific challenge as faced by the body during mercury, zinc, iron, and cadmium exposure. Daily diet and drinking habits in addition to industrial activities also form a major field of study under investigation. This study aims to investigate the role of these metals in the accumulation of pollutants in the brain, liver, and kidneys hence leading to serious consequences. Moreover, their prevalence in teenagers that are under the age of ten years is being observed that leads them to learn, writing, and intellectual abilities. Males are more affected due to their hormonal differences. The role of the GST gene in the development of cognitive conditions and its phenotypes has been discussed thoroughly in this review. The mutations of GST lead to the accumulation of peroxides and superoxides which exacerbate oxidative damage to cells. Binding of toxic metals to GSH genes and the role of glutathione transferase genes is was demonstrated in this review.

Keywords: GSH (glutathione), GST (glutathione s-transferase), toxic metals, cognitive disease, neurodegenerative diseases

1. Context

Trouble in a visual representation of two objects, thinking, learning, and memory are symptoms of a set of diseases known as cognitive diseases. These disorders include memory loss, epilepsy, autism, and other brain-related dysfunctions and are common among 2 of every 6 children born every day. Unfortunately, these disorders still do not have proper treatment at all hence may lead to permanent damage to brain tissues (1, 2). During the last few years, attention has been shifted towards the causes of these disorders and a fact came to light that chemicals are mainly responsible for causing impairment along with genetic factors that cause 30 to 50 % of disease conditions (3). Heavy metals such as mercury (Hg), lead (Pb), uranium (U), platinum (Pt), and many others have been utilized extensively in industries as chemical forms and are a serious threat to the environment and human society in

turn (4). Exposure of these metals occurs through many mechanisms including air, surface water exposure, and soil. Due to multiple sources of exposure, they can cause the most serious threats. Many trace elements present in the body are essential for the proper functioning of the autonomic system in a concentration of 0.01% but if the level increases from a certain limit, it leads to disorder conditions easily (5). They present more risk at the fetal level to babies because of weaker immune systems than that of adults and would cause changes in gene expression at later stages of life. Heavy metals are usually measured in urine, saliva, teeth, and nails as urine provides better means of accessing change in metal content of trace metals over some time (6). During the 1990s, a significant decrease in the harmful natural pollutants was seen by using a few remediation strategies but soil and water despite everything contain elevated levels of some potentially toxic elements (PTEs). Heavy metals contamination is one of the most serious dangers for the earth (7). Since the mid of the nineteenth century, the utilization of potentially harmful metals increased with resulting liberation in nature. The exact process by which metals cause toxicity is not completely known, and each metal is probably hazardous in its way. Oxidative stress and neurodegeneration, as well as dyshomeostasis in vital metal metabolism, have been described as side effects of toxic exposures to vital metals (8). The glutathione (GSH) system, thioredoxin/peroxiredoxin system, superoxide dismutases, and catalase are among the mechanisms that protect brain oxidative injury (9). Cell death is caused by an imbalance induced by high amounts of oxidant factors or lower levels of antioxidant defense mechanisms (9).

However, evidence of a putative causative or noncausal involvement of metals in human neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and autism spectrum disorder (ASD) is still scarce. The purpose of this study is to give an updated overview of the literature data on the probable association of metals and GST gene variants in the development of AD, PD, and ASD, which are the three most common neurodegenerative conditions.

2. Evidence Acquisition

To find association between metals and GST gene variants different databases such as Google Scholar, PubMed, and Scopus databases were selected to search the relevant information by using keywords including “Heavy metals”, “Neurotoxicity”, “Glutathione”, “Toxic metals AND Oxidative stress”, “Glutathione AND Metals detoxification”, and “Glutathione AND Neurodegenerative disorders”.

Only those articles were selected that included the information related to toxic metals and glutathione association in neurodegenerative disorders. Cross references of selected articles were also used to expand the search of relevant studies. Moreover, only published articles were included in this study. All other irrelevant articles were excluded that were not matched with inclusion criteria of this study. Relevant information and data were collected in 2 months.

3. Results

3.1. Glutathione and Toxic Metals Induced Oxidative Stress

The risks of human beings after exposure to toxic metals are numerous. Humans are not only exposed to heavy metals from industrial sites and environmental sources but also via medicine and dietary components. In the case of Hg, it has a strong affinity for sulfur atoms present in the endogenous thiol-containing molecule glutathione (GST). This mechanism is responsible for mercury to play a key role in the structure forming and mediating functions of both intra and extracellular membranes (10). Hg has been thought to show 10 times less attraction for oxygen-containing species and this phenomenon leads to Hg uptake, transportation, accumulation, and toxicity in brain cells. Molecular copying plays a major role in it like mimicry of Hg-GSH complex with cysteine causes easy transportation of these compounds in different organs of the body (11). Humans have a natural detoxification system in their

body that helps to get rid of these heavy metals toxins especially Hg. Oxidative stress is a condition in the body whereby humans are unable to stand with a high concentration of free radicles and reactive electrophiles formed as a result of prolonged exposure to chemicals, especially toxic metals. Transition and toxic metals can convert hydrogen peroxide to hydroxyl and hydroperoxyl, both of which are the main forms of reactive oxygen species (ROSs) that may react with biological membranes, backbones of DNA, and signaling proteins (12). Toxicity of thiol binding metals occurs at very low concentrations at molecular levels. Several experiments conducted on living organisms such as rats have demonstrated an increase in GSH concentration rather than decreasing its concentration in the body. The flux of several enzymes that are involved in sulfur binding has also increased which is a rate-limiting element for thiols. The complexes of Hg with thiol of GSH as has been discussed earlier are formed in bile and urine of model animals and are a cause of neuro and nephrotoxicity caused by oxidative stress. In the same way binding of cadmium (Cd) and other metals to thiol of GSH has been studied extensively using various biochemical techniques such as mass spectrometry etc. But arsenic (As) is a metal that shows dual behavior due to the presence of two different forms such as As(III) and As(V) (13). Its binding with thiol-containing groups can either result in cancerous condition while it also has protective functions in case of leukemia. Both forms differ in their toxicity due to methylation and As (III) is more toxic than As(V). At the chemical level, the redox potential of the body is described quantitatively as the presence of some thiol-containing compounds which coexist in both reduced and oxidative forms. Damage to biological structure occurs via the interaction of small molecules with a system having nucleophile molecules in centers of DNA and proteins resulting in the formation of toxic adducts. In other cases, reactive forms of oxygen such as hydroxyl ions, not suitable for natural systems can react with biological systems and change their physiological form (14). The resulting reaction of the biological system leads towards a condition where apoptosis, necrosis, and uncontrolled cell division occur. In the case of damage by Hg, an imbalance between thiol-containing compounds such as cysteine and GSH may occur. Hg in the case of cellular microorganism cross membrane is picked by enzymes that sandwiches Hg between thiol-containing groups making protein embedded Hg bis-thiol. Two molecules i.e., NADH and FAD act as cofactor similar to GSH reductase. The active site of enzyme hosts two cysteine of which binds to mercury and carries the bound form to the site of reduction (15). The latter process occurs as a result of oxidation of cysteine residues and the reduction of inactive enzyme using NADPH. These products cross blood-brain barriers and accumulate in the central nervous system leading to cognitive disorders such as dementia, AD, PD, and long term brain death (16).

In the case of nickel (Ni) toxicity, there are several mechanisms by which it enters the system i.e., damage to trace elements and iron (Fe) hemostasis, interaction with macromolecules, disturbance, and development of energy metabolism, and damage caused by oxidative stress. Since, after respiration Ni enters the cerebral cortex of the brain where it gathers. That's why Ni is considered the main form of toxicity in brain cells. In this case, reduced GSH activity is the most dangerous form of neuron degradation to brain cells (17). Thiol from cysteine provides glutathione with reducing power while a high concentration of it makes it the main part of the cellular system. Hence deficiency of GSH is considered a major risk for disorders such as aging, learning, and behavioral disorders, etc. Thus, oxidative damage caused by ROS species tends to activation of various transcription factors leading to activation of various inflammatory pathways. Additionally, mitochondrial DNA present in a nucleus is more susceptible to damage as compared to the mitochondrial membrane which in turn affects the coding of DNA, influencing phosphorylation thereby

altering the respiratory chain and unregulated production of reactive oxygen species, main cause of oxidative stress to cells (18).

3.2. GST's Function

GST is a family of enzymes involved in the detoxification of reactive chemical species by bonding to the reduced form of glutathione. A recent development in the field of molecular biology has enabled scientists to study large-scale genome data, expressed sequence tags, and termination signals using X-ray crystallography. Mammalian GST's have been extensively studied and been classified into various subclasses according to the given criteria but up to now, many GSTs in non-mammalian species have also been discovered. This discovery has led to the development of functions other than those that were described earlier only in mammalian species (19). These enzymes play a wide variety of functions such as removal of ROS, production of s-thiol containing proteins both of which are formed as a consequence of oxidative stress to the brain or any other cell of the body. Other generalized functions include catalysis of complexes formed because of conjugation with endogenous ligand species and in the processing of mechanisms involved in detoxification. In the case of their role in enzymatic detoxification, chemical compounds like xenobiotic and metallic species are major sources of toxicity when exposed to the human system. These toxic compounds may sometimes include phenols, aflatoxins, ROS such as superoxides, hydroxides, and superoxides. In addition to sequestration and binding, another biochemical transformation mechanism is an important pathway involved in getting rid of toxic chemical compounds (2). A healthy cell possesses a variety of enzymes responsible for the transformation of a variety of chemical structures and functions. The detoxification of xenobiotics has been classified into three distinct phases. Phases I and II involve the conversion of lipophilic compounds into more water-soluble and hence into less toxic compounds that can be easily removed from the body. Cytochrome p450 is a class of enzymes that are involved in the catalysis of such reactions in which the oxidation process occurs. Phase III involves the reactions that convert activated xenobiotics to endogenous substrates such as GSH (reduced form of glutathione), UDP glucuronic acid, and glycine. Also, they catalyze nucleophile aromatic substitutions, reduce hyper oxides resulting in the formation of oxidized glutathione which is then eliminated using several different mechanisms including ATP-dependent GS-X (glutathione S-conjugate export) pumps (20).

Moreover, GSTs are cytosolic compounds that in addition to performing the role of detoxification also have ligand binding properties. They have also been employed in various phenomena such as cancer chemotherapy, insecticide, herbicides, and microbial antibiotics. Another class of GSTs has also been identified which are quite different from others designated as membrane-associated proteins (21).

3.3. GST's Role in Toxic Metals Detoxification

In humans, Cd is usually taken up by the liver. In the liver, it binds with GSH and then can be transported to bile. In another way, it binds with metallothionein (MT) which is then used for storage purposes. Some of the Cd bound with MT also release in plasma which is then taken up by the kidney. An unbalance between bounded Cd and free Cd is the key factor of toxicity either in kidney or brain tissues. Therefore, chances of Cd toxicity depend upon the variability of enzymes related to Cd metabolism. GSTs are a group of enzymes primarily involved in the detoxification of Cd, Zn, As, aluminum (Al), Hg, and other toxic metals. The principal function of glutathione is a combination of hydrophobic and electrophilic forms with the reduced form of glutathione (22). Intracellular binding of metals with GSH is catalyzed by glutathione transferase enzymes leading to the formation of the most stable GSH –metal complexes which are then excreted outside of the body through urine and faces. Seven GSTs have been identified and genetic polymorphism has been elucidated for G*STM1*, *GSTP1*, and *GSTT1* resulting in decreased or enhanced levels of enzymatic

activity in some cases. *GSTT1* and *GSTM1* are of particular importance because of their involvement in genetic polymorphisms that results in defected catalytic activity related to greater sensitivity in the case of toxic compounds (23). Polymorphism in *GSTP1* in the region other than coding regions i.e. exon regions where it exchanges valine with isoleucine and this change is responsible for the change in enzymatic activity (24).

Increased level of As is found to be present in soil and drinking water and also diet but most commonly it enters the human body by inhalation using the nasal track. Besides human activities like industrialization, agriculture wastes, and other organoleptic changes also contribute to increasing the risk of As toxicity (19) F. During As metal exposure, the metal is trapped by GSH and cysteine residues which in turn increases sulfur requirement by induction of sulfur mechanism during exposure. Moreover, further analysis of all seven forms of GSTs found that so far only lambda form GST is involved in As stressed condition and detoxifying conditions (19). As exposure causes increased ROS and also lipid oxidation inside the body. This in turn increases glutathione concentration which using the phenomenon of feedback induction results in the activation of the glutathione transferase group of enzymes. In the case of Al, the same thing happens, and it increases glutathione which in turn activates GST transcription indicating the role of ROS species for detoxification. As Al is associated with various cognitive disorders, further researches have revealed that astrocytes are responsible for physical blood-brain barrier formation presenting glutamate and gamma-aminobutyric acid as a mean for Al toxicity in the brain (25). Another research has also revealed an inverse relationship between decreased GSH activities and an increase in neurological disorders in the case of Al. The Al-associated GST/GSH effects observed in animal models have been re-examined in human studies. For example, a study of industrial workers observed that people with the highest levels of Al in urine also have low GST enzymatic activity in erythrocytes. In the case of Hg, MeHg is a major form of toxin found in humans by consuming seafood like fish, etc. The chances of getting disease due to mercuric exposure are high at an early age as compared to young age. There exist a variety of disease symptoms in humans ranging from motor and cognitive symptoms that is more prevalent in children of age less than 14 years (25). The notion that glutathione transferase can provide MeHg-GHS complex formation has led to the discovery of many variants raised because of polymorphism in humans. Direct functional studies have revealed that GST can mediate the MeHg-GHS toxicity either directly using enzymatic activity or indirectly by knocking down of glutathione gene in them effectively. Western blotting was employed as a biochemical way of accessing their activity effectively in a biochemical way (26).

Pb exposure has thought to be the main cause of neurodegenerative diseases in humans. Numerous studies have revealed a direct relation between Pb concentration and dementia and other neuro disorders (27, 28). Oxidative stress is a mechanism by which Pb affects brain learning ability, IQ, and other such functions. It has been described in previous studies that in vulnerable neurons of AD patient's lipid peroxidation, nitrotyrosine, reactive carbonyls, and nucleic acid oxidation observed to be increased as compared to control patients, irrespective of whether individual neurons contain AD pathology (29, 30). Consequently, symptoms of oxidative damage lead to other pathological issues in AD and is an early event in the disease pathogenesis (31). GST in this case is the compound involved in the protection of harmful chemicals including radicles which in this case results in phenotypic variations among genes. Of all the polymorphic forms, persons that are not having the gene GSTM1 showed greater exposure to Pb and in turn more symptoms related to brain disorders. Bones may be considered as the best matrix for the estimation of Pb having a half-life of more than a month or two (32).

3.4. GST Gene Variants Related to Toxic Metal-Induced Neuron Degradation

Heavy metals or trace metals are found everywhere on earth and because of this, they are responsible for most of the diseases in the body including neuron degradation, etc. Because of their presence in the environment, people who are not exposed to them at any point in their life are also at risk of being affected by a trace amount of them through their food, environment, and organoleptic activities. Trace amounts of metals such as copper (Cu), Zn, and Fe are essential for the body including for some enzymatic activities. Others such as Cd, Hg, and Pb are toxic to humans and can be a way leading to brain death and permanent loss because they can cross the blood-brain barrier and causing enzymatic changes or oxidative damage stress. Glutathione related genes also known as glutathione transferase are a group of an enzyme that binds with GHS in its reduced form and also binds with a substrate of xenobiotic (33). This mechanism leads to the solubility of water and its detoxification from the body. GST family consists of various forms of polymorphic genes such as alpha, beta, gamma, mu, theta, and sigma all of which show more or less than 45% of homology in one or two aspects. However, most of them are showing polymorphism that tends to show dissimilarity in enzymatic activity of enzymes among different numbers of populations (34). For example, two SNPs in the case of GSTP1 show two polymorphic forms i.e., Ile105Val and Ala114Va both of them are associated with altered enzymatic activity and substrate binding by these enzymes. These variations result in a condition where the mechanism involved in the transportation of Hg binding conjugates is disturbed and leads to a disease condition. GSTT1 and GSTM1 are some types of GST polymorphisms in which deletion mutation in their encoding sequence causes the impaired enzymatic activity. Impaired enzymatic activity is associated with more sensitivity to toxic substances in long term (35). In the case of MeHg, intoxication results because of eating fish were examined in two groups including control and sample groups. Results revealed the fact that polymorphism has been shown to display a direct relationship between the amount of polymorphism and uptake of bounded Hg by red blood cells such as erythrocytes. Patients with V allele of polymorphic form have shown to contain less bounded Hg than that of other forms of Hg and other heavy metals. Also, all other genetic polymorphic forms are thought to be indicative of glutathione present in urine, plasma, and blood, etc., including allelic forms of GSTT1, GSTM1, and GSTP1 Val105Ile (36).

3.4.1. Parkinson’s Disease (PD)

Parkinson's disease (PD) is a cerebrum issue that prompts shaking, solidness, and trouble with strolling, parity, and coordination. Parkinson's side effects ordinarily start progressively and begin to get complex after some time. As the disease advances, individuals may experience issues strolling and talking. They may likewise have mental and behavioral changes, mood issues, sorrow, memory challenges, and weakness. The disease affects around 50% more men than ladies (37). One obvious risk factor for PD is age. Although many people with PD initially build up the disease at about age 60, around 5 to 10% of individuals with PD have "beginning stage" illness, which starts before the age of 50. Early-stage types of PD are, however not generally, acquired, and a few structures have been connected to explicit quality transformations (38).

PD usually happens when nerve cells, or neurons, in a territory of the brain that controls development become impeded or potentially die. Regularly, these neurons produce a significant cerebrum chemical known as dopamine. At the point when the neurons die or become debilitated, they produce less dopamine, which causes the development issues as in the case of PD. Researchers despite everything don't have a clue what causes cells that produce dopamine to die. Researchers are attempting to comprehend the typical and irregular elements of alpha-syncline and its relationship to hereditary changes that form the basis of PD dementia (39). Although a few instances of PD give off an impression of being inherited, and a couple can be

followed to explicit genetic mutations, as a rule, the disease happens randomly and doesn't appear to run in families. Numerous analysts presently accept that PD results from a mix of hereditary components and natural factors. For example, exposure to toxic metals such as Pd, Hg, etc. Research has depicted the role of GST genes and their variants involved in PD such as allelic variants *GSTO1, GSTO2*. These variants play important role in studying the effect caused by the presence of reactive oxygen species such as superoxides and hydroxyls which formed as a result of oxidative damage or stress in a tissue or body. Oxidative stress activates GST to detoxify many products formed as a result of detoxification, lipid, nucleic acid, and protein oxidation (40).

3.4.2. Alzheimer's Disease (AD)

Alzheimer's Disease (AD) is an irreversible, dynamic brain issue that gradually annihilates memory and thinking aptitudes and, in the long run, the capacity to do the simplest assignments. In the vast majority with the illness-those with the late-beginning sort—side effects initially show up in their mid-60s. Beginning stage AD happens between an individual's 30s and mid-60s and is exceptionally uncommon. Ad is the most well-known reason for dementia among more well-known grown-ups (41). The plaques and tangles in the cerebrum are as yet thought to be a part of the fundamental key factors of AD. Another element is the loss of associations between nerve cells (neurons) in the cerebrum. Neurons transmit messages between various parts of the cerebrum, and from the mind to muscles and organs in the body. Numerous other complex mind changes are thought to play role in Alzheimer's, as well. This harm at first seems to happen in the hippocampus, the part of the brain involved in framing memories. People who take part in reading exercises, for example, perusing, playing prepackaged games, finishing crossword puzzles, playing instruments, or standard social collaboration show a reduced risk for AD (42). This is perfect with the intellectual hold hypothesis, which expresses that some beneficial encounters bring about progressively proficient neural working giving the individual a psychological save that postpones the beginning of dementia manifestations. Education defers the beginning of AD disorder without changing the length of the disease. Learning a subsequent language considerably further down the road appears to defer the beginning of AD. Physical movement is likewise connected with a diminished danger of AD. Physical exercise is related to the diminished pace of dementia. Physical exercise is additionally successful in decreasing indication seriousness in those with AD (43).

Individuals who keep up a sound, Japanese, or Mediterranean eating routine have a diminished danger of AD. The Mediterranean eating regimen may improve results in those with the disease. Those who eat an eating routine high in immersed fats and basic starches (mono-and disaccharide) have a higher risk. The Mediterranean eating regimen's gainful cardiovascular impact has been proposed as the system of activity. The reasons for AD are perplexing yet there is a general understanding of the presence of a connection between AD and oxidative stress (44). The GSTs act to detoxify the results of oxidation that cause harm to macromolecules. Specific consideration has been centered on GST qualities since polymorphisms are significant determinants of ailment chance. The GSTM1 chemical detoxifies substances, for example, exogenous and endogenous metabolites, and assumes a regulatory role in cell signaling. Past investigations have featured that GSTM1 has a job in neurodegenerative disorders, however, no information has related the GSTM1 relation with AD hazard. Results proposed that the GSTM1 null genotype is a hazard factor for AD in Italian patients (45).

3.4.3. Autism Spectrum Disorders (ASD)

Autism is a formative issue resulted from troubles with social association and correspondence, and by restricted and repetitive behavior. Parents regularly notice signs during the initial three years of their

youngster's life. These signs frequently grow slowly, however a few kids with mental imbalance experience difficulty in their correspondence and social abilities in the wake of arriving at formative achievements at an ordinary pace. Chemical imbalance is related to an intermix of hereditary and natural factors (46). Risk factors during pregnancy incorporate certain contaminations, for example, rubella, poisons including corrosive, liquor, cocaine, pesticides, Pb, and air contamination, fetal development limitation, and immune system diseases. Controversies are present for other proposed ecological causes; for instance, the vaccine immunization, which has been disproven. Autism influences information handling in the mind and how nerve cells and their neural connections associate and sort out; how this happens isn't well understood. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5), consolidates autism and less extreme types of the condition, including Asperger disorder and pervasive developmental disorder not otherwise specified (PDD-NOS) into the analysis of ASD. The primary objectives while treating kids with chemical imbalance are to decrease related shortages and family trouble and to build personal satisfaction and practical freedom (47). By and large, higher IQs are related to more prominent responsiveness to treatment and improved treatment outcomes. Families and the instructive framework are the primary resources for treatment. Services should be conducted by experts, specialized curriculum educators, discourse pathologists, and authorized analysts. Prescriptions might be utilized to treat ASD manifestations that meddle with coordinating a youngster into home or school when social treatment fails (48). They may likewise be utilized for related medical issues, for example, ADHD or anxiety. More than half of US kids determined to have ASD are recommended psychoactive medications or anticonvulsants, with the most widely recognized medication classes being antidepressants, energizers, and antipsychotics.

Members of the GST gene family play a major role in combatting symptoms of the disease by reducing the effects of oxidative damages via conjugation of GSH genes with many toxic metals. The results from a study conducted under high supervision have suggested the involvement of the polymorphism of the GST gene in the treatment of disease symptoms (49). For example, haplotype consisting of two polymorphisms in the *GSTP1* gene (Ile105Val and Ala114Val) was significantly over-transmitted to the mothers during pregnancy and early age of fetal tissues. Hence there exists a close association of toxicity that is caused due to the accumulation of toxic metals i.e., Hg, Pb, Al, As, etc. Also, the role of the GST gene and its variants in relieving effects of oxidative damage and function is performed by either of these alleles such as *GSTT1*, *GSTM1*, *GSTP1*(50).

3.4.4. Other Neurodegenerative Disorders

Multiple sclerosis (MS) is a conceivably debilitating illness of the brain and spinal cord (focal sensory system). In MS, the defensive immune system assaults the sheath (myelin) that spreads all around nerve strands and disturbs communication between the brain i.e., the central nervous system and the remaining body. In the long run, the disease can cause permanent harm or crumble of the nerves. Signs and indications of MS fluctuate broadly and rely upon the measure of nerve harm and which nerves are influenced. A few people with serious MS may lose the capacity to walk autonomously or by any means, while others may encounter a long period of remission with no new manifestations (51). There's no treatment present for MS, however, treatment can help speedy recovery from disease, alter the course of the disease, and oversee symptoms. GSH is acting as a cofactor in all of the research for the enzyme that is involved in the detoxification process named GST. Among all other variants of GST, GSTM1 and GSTT1 are linked to loss of brain function caused actually due to MS (52).

Dementia is a general term for ailments and conditions described by a decrease in memory, language, critical thinking, and other reasoning aptitudes that influence an individual's capacity to perform regular exercises. Memory loss is a model.

Alzheimer's is the most well-known reason for dementia. Dementia is anything but a solitary infection; it's a general term-like coronary illness- that covers a wide scope of brain disorders, including AD. All of the neurological disorders that come under the general term "dementia" are brought about by irregular cerebrum changes (53). These progressions trigger a decrease in speculation aptitudes, otherwise called intellectual capacities, sufficiently serious to debilitate day by day. They additionally influence conduct, emotions, and relationships. Dementia is brought about by harm to synapses. This harm meddles with the capacity of the brain to communicate with the whole body. At the point when the brain can't impart ordinarily, figuring, conduct, and emotions can be influenced. The cerebrum has numerous portions, every one of which is answerable for various capabilities (for instance, memory, judgment, and development). At the point when cells in a specific area are harmed, that area can't do its capacities normally (54). Recently, oxidative stress due to heavy metal accumulation, damage to mitochondrial DNA has been studied. Moreover, it has been found that the GSH gene is responsible for reducing the toxicities when its cofactor reacts with metal ions in a specific part of the brain (55).

4. Conclusions

Over the last few decades, the interest of scientists has been shifted towards brain-related disorders and the use of metals in their toxicities. In this context, a huge source of research was attributed to the study of these metals. It comes forward as a fact that most of the damage to the brain caused by exposure to metallic compounds occurs during pregnancy or postnatal stage where there may result in permanent brain damage or loss of brain activity. Molecular mechanisms by which metals trigger these reactions are still unclear but the involvement of the GST gene in down-regulation of AD result in diminishing the effects of oxidative stress and the formation of conjugation complex resulted from a combination of metallic ion and glutathione which is a substrate for a gene. It can also be concluded that males are more prone to it than that females as male-related hormones such as testimonies tend to enhance the effect of the metal ion exposure in some cases. Metals like Pd, Hg, and Cu tend to interact at physiological and hormonal levels. The reduction of exposure to metal ion sources during parental and postnatal periods would prove to be an effective way of reducing the disastrous effects caused by them. Use of properly cleaned water, vegetables are grown in soil free from contaminants, and changing our daily routine of exposure will prove to be very helpful.

Authors' Contribution

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

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Acharya R, Lim C, Joseph P. Heart rate variability analysis using correlation dimension and detrended fluctuation analysis. Itbm-Rbm. 2002;23(6):333-9.
2. Mihalopoulos C, Vos T, Rapee RM, Pirkis J, Chatterton ML, Lee YC, et al. The population cost- effectiveness of a parenting intervention designed to prevent anxiety disorders in children. J Child Psychol Psychiatry. 2015;56(9):1026-33.
3. Galaska R, Makowiec D, Dudkowska A, Koprowski A, Chlebus K, Wdowczyk- Szulc J, et al. Comparison of wavelet transform modulus maxima and multifractal detrended fluctuation analysis of heart rate in patients with systolic dysfunction of left ventricle. Ann Noninvasive Electrocardiol. 2008;13(2):155-64.
4. Bolognin S, Messori L, Zatta P. Metal ion physiopathology in neurodegenerative disorders. Neuromolecular Med. 2009;11(4):223-38.

5. Uversky VN, Li J, Fink AL. Metal-triggered structural transformations, aggregation, and fibrillation of human α-synuclein a possible molecular link between parkinson′ s disease and heavy metal exposure. J Biol Chem. 2001;276(47):44284-96.
6. Rahimzadeh MR, Rahimzadeh MR, Kazemi S, Moghadamnia A-a. Cadmium toxicity and treatment: An update. Caspian J Intern Med. 2017;8(3):135.
7. Matés JM, Segura JA, Alonso FJ, Márquez J. Roles of dioxins and heavy metals in cancer and neurological diseases using ROS-mediated mechanisms. Free Radic Biol Med. 2010;49(9):1328-41.
8. Martinez-Finley EJ, Gavin CE, Aschner M, Gunter TE. Manganese neurotoxicity and the role of reactive oxygen species. Free Radic Biol Med. 2013;62:65-75.
9. Bell KF, Al-Mubarak B, Martel M-A, McKay S, Wheelan N, Hasel P, et al. Neuronal development is promoted by weakened intrinsic antioxidant defences due to epigenetic repression of Nrf2. Nat Commun. 2015;6(1):1-15.
10. Silverman WK, Kurtines WM, Ginsburg GS, Weems CF, Lumpkin PW, Carmichael DH. Treating anxiety disorders in children with group cognitive-behavioral therapy: A randomized clinical trial. J Consult Clin Psychol. 1999;67(6):995.
11. Barrett PM, Duffy AL, Dadds MR, Rapee RM. Cognitive–behavioral treatment of anxiety disorders in children: Long-term (6-year) follow-up. J Consult Clin Psychol. 2001;69(1):135.
12. Compton SN, March JS, Brent D, Albano AM, Weersing VR, Curry J. Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. J Am Acad Child Adolesc Psychiatry. 2004;43(8):930-59.
13. Landgren M, Svensson L, Strömland K, Grönlund MA. Prenatal alcohol exposure and neurodevelopmental disorders in children adopted from eastern Europe. Pediatrics. 2010;125(5):1178-85.
14. Dodd B, Leahy J, Hambly G. Phonological disorders in children: Underlying cognitive deficits. Br J Dev Psychol. 1989;7(1):55-71.
15. Last CG, Hersen M, Kazdin A, Orvaschel H, Perrin S. Anxiety disorders in children and their families. Arch Gen Psychiatry. 1991;48(10):928-34.
16. Kendall PC. Treating anxiety disorders in children: results of a randomized clinical trial. J Consult Clin Psychol. 1994;62(1):100.
17. Chalfant AM, Rapee R, Carroll L. Treating anxiety disorders in children with high functioning autism spectrum disorders: A controlled trial. J Autism Dev Disord. 2007;37(10):1842-57.
18. Last CG, Perrin S, Hersen M, Kazdin AE. DSM-III-R anxiety disorders in children: Sociodemographic and clinical characteristics. J Am Acad Child Adolesc Psychiatry. 1992;31:1070.
19. James AC, James G, Cowdrey FA, Soler A, Choke A. Cognitive behavioural therapy for anxiety disorders in children and adolescents. Cochrane Database Syst Rev. 2013;(6).
20. Currie J, Stabile M. Mental health in childhood and human capital. The problems of disadvantaged youth: An economic perspective: University of Chicago Press; 2007. p. 115-48.
21. Meadows P, Melhuish E. National evaluation of Sure Start local programmes: An economic perspective. 2011.
22. Mihalopoulos C, Vos T, Pirkis J, Carter R. The economic analysis of prevention in mental health programs. Annu Rev Clin Psychol. 2011;7:169-201.
23. Van Steensel FJ, Bögels SM, Perrin S. Anxiety disorders in children and adolescents with autistic spectrum disorders: a meta-analysis. Clin Child Fam Psychol Rev. 2011;14(3):302.
24. In-Albon T, Schneider S. Psychotherapy of childhood anxiety disorders: A meta-analysis. Psychother Psychosom. 2007;76(1):15-24.
25. Ipser JC, Stein DJ, Hawkridge S, Hoppe L. Pharmacotherapy for anxiety disorders in children and adolescents. Cochrane Database Syst Rev. 2009;(3).
26. Wehry AM, Beesdo-Baum K, Hennelly MM, Connolly SD, Strawn JR. Assessment and treatment of anxiety disorders in children and adolescents. Curr Psychiatry Rep. 2015;17(7):52.
27. Killin LO, Starr JM, Shiue IJ, Russ TC. Environmental risk factors for dementia: a systematic review. BMC Geriatr. 2016;16(1):1-28.
28. Power MC, Adar SD, Yanosky JD, Weuve J. Exposure to air pollution as a potential contributor to cognitive function, cognitive decline, brain imaging, and dementia: a systematic review of epidemiologic research. Neurotoxicology. 2016;56:235-53.
29. Castellani RJ, Harris PL, Sayre LM, Fujii J, Taniguchi N, Vitek MP, et al. Active glycation in neurofibrillary pathology of Alzheimer disease: Nε-

(carboxymethyl) lysine and hexitol-lysine. Free Radic Biol Med. 2001;31(2):175-80.
30. Nunomura A, Perry G, Aliev G, Hirai K, Takeda A, Balraj EK, et al. Oxidative damage is the earliest event in Alzheimer disease. J Neuropathol Exp Neurol. 2001;60(8):759-67.
31. Bonda DJ, Wang X, Perry G, Nunomura A, Tabaton M, Zhu X, et al. Oxidative stress in Alzheimer disease: a possibility for prevention. Neuropharmacology. 2010;59(4-5):290-4.
32. Thulin U, Svirsky L, Serlachius E, Andersson G, Öst L-G. The effect of parent involvement in the treatment of anxiety disorders in children: A meta-analysis. Cogn Behav Ther. 2014;43(3):185-200.
33. Lebowitz ER, Omer H, Hermes H, Scahill L. Parent training for childhood anxiety disorders: the SPACE program. Cogn Behav Pract. 2014;21(4):456-69.
34. Chavira DA, Golinelli D, Sherbourne C, Stein MB, Sullivan G, Bystritsky A, et al. Treatment engagement and response to CBT among Latinos with anxiety disorders in primary care. J Consult Clin Psychol. 2014;82(3):392.
35. Silverman WK, Kurtines WM, Jaccard J, Pina AA. Directionality of change in youth anxiety treatment involving parents: an initial examination. J Consult Clin Psychol. 2009;77(3):474.
36. Kendall PC, Peterman JS. CBT for adolescents with anxiety: Mature yet still developing. Am J Psychiatry. 2015;172(6):519-30.
37. Cummings JL. Depression and Parkinson's disease: a review. Am J Psychiatry. 1992.
38. Limousin P, Krack P, Pollak P, Benazzouz A, Ardouin C, Hoffmann D, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med. 1998;339(16):1105-11.
39. Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med. 2006;355(9):896-908.
40. Mallet L, Mesnage V, Houeto J-L, Pelissolo A, Yelnik J, Behar C, et al. Compulsions, Parkinson's disease, and stimulation. Lancet. 2002;360(9342):1302-4.
41. Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med. 2010;362(22):2077-91.
42. Houeto J, Mesnage V, Mallet L, Pillon B, Gargiulo M, Du Moncel ST, et al. Behavioural disorders, Parkinson's disease and subthalamic stimulation. J Neurol Neurosurg Psychiatry. 2002;72(6):701-7.
43. Krack P, Pollak P, Limousin P, Hoffmann D, Xie J, Benazzouz A, et al. Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. Brain. 1998;121(3):451-7.
44. Thaut MH, McIntosh GC, Rice RR, Miller RA, Rathbun J, Brault J. Rhythmic auditory stimulation in gait training for Parkinson's disease patients. Mov Disord. 1996;11(2):193-200.
45. Løvås K, Husebye ES. High prevalence and increasing incidence of Addison's disease in western Norway. Clin Endocrinol. 2002;56(6):787-91.
46. Soule S. Addison's disease in Africa—a teaching hospital experience. Clin Endocrinol. 1999;50(1):115-20.
47. Jódar E, Valdepeñas MPR, Martinez G, Jara A, Hawkins F. Long-term follow-up of bone mineral density in Addison's disease. Clin Endocrinol. 2003;58(5):617-20.
48. Masliah E, Ellis RJ, Mallory M, Heaton RK, Marcotte TD, Nelson JA, et al. Dendritic injury is a pathological substrate for human immunodeficiency virus—related cognitive disorders. Ann Neurol. 1997;42(6):963-72.
49. Wiley JC, Pettan-Brewer C, Ladiges WC. Phenylbutyric acid reduces amyloid plaques and rescues cognitive behavior in AD transgenic mice. Aging Cell. 2011;10(3):418-28.
50. Caballol N, Martí MJ, Tolosa E. Cognitive dysfunction and dementia in Parkinson disease. Mov Disord. 2007;22(17):358-66.
51. Hock C, Golombowski S, Naser W, MüLler-Spahn F. Increased levels of τ protein in cerebrospinal fluid of patients with alzheimer's disease—correlation with degree of cognitive impairment. Ann Neurol. 1995;37(3):414-5.
52. Wiley CA, Achim C. Human immunodeficiency virus encephalitis is the pathological correlate of dementia in acquired immunodeficiency syndrome. Ann Neurol. 1994;36(4):673-6.
53. Finkel S. Introduction to behavioural and psychological symptoms of dementia (BPSD). Int J Geriatr Psychiatry. 2000;15(1):2-4.
54. Hepburn KW, Tornatore J, Center B, Ostwald SW. Dementia Family Caregiver Training: Affecting Beliefs About Caregiving and Caregiver Outcomes. J Am Geriatr Soc. 2001;49(4):450-7.

55. Bathgate D, Snowden JS, Varma A, Blackshaw A, Neary D. Behaviour in frontotemporal dementia, Alzheimer's disease and vascular dementia. Acta Neurol Scand. 2001;103(6):367-78.