

The Role of Lead in Neurotoxicity - A Recent Review

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Abstract: *Lead in the environment rarely occurs in its elemental state but rather in its +2 oxidation state (Pb²⁺) in various ores throughout the earth. It Provide in the role of early environmental exposure to lead in the development of adult-onset psychiatric disorder. Knowledge of the neurotoxicology of lead has advance in recent decades do due revelations regarding mechanisms and cellular specificity of lead.*

Keywords: Lead, Lead Exposure, Children Health, Neurotoxicology

Lead is a chemical element with the symbol Pb (from the Latin *plumbum*) and atomic number 82. Lead (Pb), is a dull, silvery white or grayish metal. It is a heavy metal that is denser than most common materials. Lead is soft and malleable and also has a relatively low melting point. Lead (Pb) is a highly toxic heavy metal occurring naturally in the Earth's crust.

Lead is found in all parts of the environment. Lead exists in three forms: metallic lead, inorganic lead and lead compounds (or lead salts), and organic lead (containing carbon). Lead in the environment rarely occurs in its elemental state but rather in its +2 oxidation state (Pb²⁺) in various ores throughout the earth. [1]. It is a metal that has been used since Roman times for making paints and pipes as a corrosion resistant. It used in car batteries and a major ingredient of lead acid batteries. It is also use in soldering parts of electrical equipment and electrodes in electrolysis processes.

The lead exposure is a public health concern, especially in early childhood as children are more at risk because of increased hand to mouth activity and absorb about half of an oral dose of water-soluble lead [2]. Childhood lead exposure is estimated to contribute to 600,000 new cases of children with intellectual disabilities every year with 99 % of them living in developing countries [3]. The lead exposure in utero, infancy or early childhood can slow mental development and cause lower intelligence later in childhood that can persist beyond childhood. The effects of lead are more toxic on developing nervous system of children than on a mature brain. Lead-associated deficits have been documented in most fields including verbal intelligence quotient (IQ), performance IQ, academic skills such as reading and mathematics, visual/spatial skills, problem-solving skills, executive functions, fine and gross motor skills, memory and language skills. Meta-analyses have indicated those children's IQ scores decline 2–3 points per 10 µg/dl increase in blood lead level. In fact academic performance of children exposed to lead has been observed to be subservient in comparison to controls. Children (6–10 year old) with blood lead levels of 5–10 µg/dl scored

significantly lower than children with levels of 1–2 µg/dl on academic skills such as word reading, reading comprehension, listening comprehension, math reasoning and math calculations [4]. Another large American study documented inverse association between blood lead levels as low as 2 µg/dl, measured up to 5 years of age, and end-of grade reading and mathematics achievement scores [5]. In National Health and Nutrition Examination Survey (1999–2002), the risk of parent-reported diagnosis of attention deficit hyperactivity disorder increased, in a dose dependent manner with blood lead level [4]. Similar findings have been reported by a recent Indian study which emphasizes the detrimental effect of lead on executive and attention domain in neurobehavioral function [6]. The mechanisms underlying lead-induced neurotoxicity are complex. Oxidative stress, membrane bio-physics alterations, deregulation of cell signaling, and the impairment of neurotransmission are key aspects involved in lead neurotoxicity. It can cause toxicity by oxidative stress directly or indirectly by lipid peroxidation resulting in the generation of reactive oxygen species (ROS), including hydroperoxides, singlet oxygen, hydrogen peroxide and direct depletion of antioxidant reserves. Lead renders enzymes nonfunctional by binding to their sulfhydryl groups further contributing to impairment in oxidative balance [7]. The ability of lead to pass through the blood–brain barrier is mainly due to its ability to substitute for calcium ions. Within the brain, lead-induced damage in the prefrontal cerebral cortex, hippocampus, and cerebellum can lead to a variety of neurological disorders, such as brain damage, mental retardation, behavioral problems, nerve damage, and possibly Alzheimer's disease, Parkinson's disease and schizophrenia [8].

Lead substitutes for calcium and to a lesser extent zinc, inappropriately triggers processes dependent on calmodulin. Lead also restricts neurotransmitter release, disrupting the function of GABAergic, dopaminergic and cholinergic systems ATPase thus interfering with energy metabolism. Within the cell, lead appears to interfere with calcium release from the mitochondria resulting in formation of permeability transition pore and primes for programmed cell death processes leading to mitochondrial self-destruction.

New research provides convincing evidence that exposures to lead have adverse effects on the central nervous system (CNS), that environmental factors augment lead susceptibility, and that exposures in early life can cause neurode-generation in later life. As the main target for lead toxicity is the CNS, the brain is the organ most studied in lead toxicity. Lead neurotoxicity occurs when the exposure to lead alters the normal activity of the CNS and causes damage to the CNS. The direct neurotoxic actions of lead include apoptosis (programmed cell death), excitotoxicity affecting neurotransmitter storage and release and a modifying neurotransmitter receptors, mitochondria, second messengers, cerebrovascular endothelial cells, and both astroglia and oligodendroglia. Symptoms can appear immediately after exposure or may be delayed and include loss of memory, vision, cognitive and behavioral problems, and brain damage/mental retardation.

Most early studies concentrated on the neurocognitive effects of lead, but recently higher exposures have been associated with such morbidities as antisocial behavior, delinquency, and violence. Several hypotheses have been proposed to explain the mechanism of lead toxicity on the

CNS. As such, these people need special attention and protection. It is of public health importance to figure out which allele is the susceptible one and how it operates in the human body. The human data available on chelation efficacy suggest that primary prevention of exposure is the best strategy for limiting lead-associated neurodevelopmental morbidity.[9-10]

In Nigeria, Lead and cadmium were found to be significantly increased in newly diagnosed drug-free schizophrenic patients compared with controls according to Arinola *et al.* (2010). Thus, a mechanism that will decrease blood lead level may be helpful in the management of schizophrenia.

Various studies using different research designs have implicated increased bone and blood lead levels with different forms of psychiatric conditions ranging from depression, schizophrenia, bipolar disorder, mood disorders, etc. All the studies associated depression, schizophrenia, and bipolar disorder with significant increases in the body burden of lead.[11-16]

Authors	Study Design	Finding	Ref no.
oplert et al., 2008	241 pooled matched sets of cases and controls from both the California and New England sites using a multilevel random-intercept logistic regression model	Provided further evidence for the role of early environmental exposure to lead in the development of adult-onset psychiatric disorder.	11
Bouchard et al.,2010	Cross-sectional epidemiology survey. A total of 1987 adult age 22 to 39 years who responded to the National Health and nutrition examination survey (1999 – 2004).	Low level of lead exposure, higher blood lead levels were associated with increased odds of major depression and panic disorders	12
Arinola at al., 2010	20 healthy volunteers (controls) and 35 schizophrenic patients	lead was significantly rise in newly diagnosed drug free schizophrenic patients compared with controls	13
Godzalez - Estechea at al., 2011	25 hospitalized patients diagnosed with bipolar disorder matched with 29 healthy controls without psychiatric disorders.	increased blood and urine lead in bipolar disorders	14
Eum at al., 2012	Nurses' Health Study (NHS) cohort. 617 nurse participants.	Associated of low-level cumulative lead exposure with increased depressive and phobic anxiety symptoms among older women	15
Macfarlane at al., 2013	prospective cohort	Associations between early lead exposure and emotional/behaviour functioning in children might persist into adulthood, at least for females.	16

Knowledge of the neurotoxicology of lead has advanced in recent decades due to revelations regarding the mechanisms and cellular specificity of lead. Potential mechanisms of lead-induced cognitive deficits have been investigated using cellular models of learning and memory. New research provides convincing evidence that exposures to lead have adverse effects on the central nervous system (CNS), that environmental factors augment lead susceptibility, and that exposures in early life can cause neurode-generation in later life.

Lead pervades almost every organ and system in the human body, but the main target for lead toxicity is the CNS, both in adults and in children. Blood is the most common tissue used as a biomarker of lead exposure although many other tissues and body fluids including the bone, hair, nail, saliva, tooth, urine, and umbilical cord blood have been considered. Lead is more toxic in young and unborn children than in older children and adults. In children, lead poisoning has been associated with brain damage, mental retardation, behavioral problems, developmental delays, violence, and

death at high levels of exposure. The metal has also been related to the damage of sense organs and nerves controlling the body, impaired cognitive function, as well as hearing and vision impairment in adults. Studies have shown that lead exposure in children persists into adulthood. Experimental studies with animals have shown that lead exposure causes genotoxic effects, especially in brain, bone marrow, lung, and liver cells.[17]

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